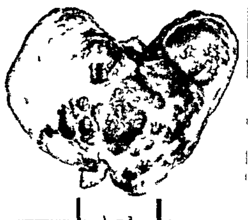


Subacut necr is of th liver due to h molog us crum h patitis Se al o Fig 4 page 6



Post necrotic cirrhosis du to inf ctiou s hepat tis

DISEASES
of the
LIVER

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to Anna and Victor Michael

Since the liver was considered the seat of life it of all the organs was attuned to the will and designs of the gods Hence, reading the liver was believed to disclose the secrets of the divine mind (2000 B C)

M Jastrow

FOREWORD

STRANGE as it may seem the liver with its relatively simple architecture is one of the most puzzling organs in the body. To some it may seem wrong to rank the liver ahead of the brain—the mysteries of which elude us so completely—but the brain is admittedly a complex structure. The liver has only one specific cell, the polygonal cell, and yet within it scores if not hundreds of different chemical processes are known to take place. The magnitude of our ignorance of the liver may be illustrated by the fact that it is the only organ in the body whose experimental removal causes death for reasons as yet unknown (Ivy). Similarly the mechanism of death from hepatic coma is most obscure. Even the significance and cause of fetor hepaticus are still controversial. Perhaps it is not surprising therefore that to many medical students and practitioners the liver is simply a large organ in the right upper abdomen, physiologically concerned with digestion and clinically troublesome because of the production of gall stones, distension of the capsule in heart failure, enlargement with metastatic neoplasm, or because of ascites or bleeding esophageal varices secondary to cirrhosis—beyond which the liver is a sort of no man's land.

It is fortunate indeed that Dr Spellberg has ...en fit to assemble so beautifully in this volume ...ch a mass of knowledge of the liver—its ...ucture, function and derangement in dis...e. The thoroughness of his work is evident ...m the fact that nothing seems to have been ...itted. The bibliography of approximately ...o references testifies to the exhaustiveness of ... study and makes it possible for those who ... to examine original data in greater detail ...d their sources quickly. ... Spellberg points out that the clinician has three approaches to the study of hepatic disease: through clinical study and observation, through anatomic material now provided by means of needle or other biopsy, and through physiologic methods (the so-called liver function tests). The comprehensive discussion of the clinical aspects of hepatic disease and the manner in which the liver is affected by a multitude of diseases and disorders shows that the author is an astute clinician and a master of the subject. Recent developments in the correlations between structure and function are well presented in the sections dealing with needle biopsy and the tests of hepatic function. Dr Spellberg has described all of the significant tests of hepatic function and has shown carefully the manner in which the information gained from them may be applied at the bedside. The sections on differential diagnosis are excellent and provide the reader with a vast fund of information regarding all manner of disease—infectious, parasitic, toxic, neoplastic and otherwise. The therapy of hepatic disease is amply discussed with clear explanations of basic principles and reasons. The brief summaries in bold type at the end of each section will be greatly appreciated by those wishing to find or digest quickly the most important information on any one subject.

It is a pleasure to congratulate Dr Spellberg and to express appreciation for this splendid compilation so ably presented of the existing knowledge of that most mysterious organ, the liver.

University of Chicago
Department of Medicine
February 1954

WALTER L PALMER

PREFACE

IN THE LAST DECADE much attention has been *focused on the experimental and clinical* aspects of diseases of the liver This attention is warranted because of the frequency of hepatic diseases in clinical practice and the all important relationship of the liver to other diseases and other organs The literature on the subject has become enormous The multiplication of publications and investigators and the dynamic state of our knowledge inevitably result in contradictions conflicts and confusion A busy practitioner of medicine regardless of his ability and good intentions may find it impossible to gain a clear perspective of the subject The numerous classifications of jaundice and cirrhosis serve to confuse rather than clarify

This book is written from the viewpoint of a clinician for clinicians It is hoped that it will be of help in dispelling the mist that envelops many problems in hepatology With this in mind the ancient literature and historical data is either completely eliminated or utilized only when it is of current significance There is no *separate section on physiology or anatomy* but these subjects are discussed as they relate to diagnosis and treatment

Emphasis throughout the book is on the triple spearheads for diagnosis clinical biochemical (physiologic) and anatomic factors Intelligent recognition and treatment of diseases of the liver can be accomplished only by looking for the cause and the resulting physio*logic and anatomic alterations* It is proposed that the diagnosis of cirrhosis should contain a reference to etiology to anatomic alterations and to physiologic defects

The author takes this opportunity to express his gratitude to the numerous colleagues associates students and patients who intentionally or fortuitously contributed ideas for the book The students interns and residents encountered at the University of Illinois Michael Reese Hospital and Hines Veterans Administration Hospital by asking questions and demanding concise answers have helped to crystallize the organization of the book Special thanks are due to the wise clinician Dr Robert W Keeton who kindled my interest in the liver nearly twenty years ago and to Dr Samuel Soskin at whose suggestion the book was conceived I am grateful to Dr Harry F Dowling for valuable suggestions Dr Rachmiel Levine graciously reviewed some sections of the book and offered valuable and constructive criticism I have received much help from the pathology departments illustration and photographic studios of the University of Illinois Michael Reese Hospital and Hines Veterans Administration Hospital I am especially grateful to Dr Otto Saphir and Dr Conrad L Pirani who permitted the use of some of their pathologic specimens Mr *Tom Jones* and *Tom Fung have been of* great help in developing the illustrations Special thanks are due to the librarians at the University of Illinois and Michael Reese Hospital for their unstinted aid Miss Jean Wilson did an excellent job in typing the manuscript William Spellberg gave invaluable assistance in preparing the tables and arranging the bibliography Without my wife s encouragement patience and forbearance this task would have been insurmountable

M A SPELLBERG

Chicago
February 1954

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THE clinician has three methods at his disposal to help him to determine the presence and the severity of liver disease in a given patient (1) the clinical approach consisting of symptoms and physical findings (2) the anatomical approach consisting of an analysis of the structural changes and (3) the physiological approach consisting of an evaluation of the biochemical and physiological alterations The first of these is the jumping off place—the starting point—of all clinicians and needs no elaboration here The second or anatomical approach was in the past relegated chiefly to the autopsy table but now with the increasing use of needle biopsy this viewpoint has become dynamic and applicable to clinical problems (Chapter 10 page 48)

The third or physiological approach is most important for the understanding of the individual clinical problem as ... broader aspects

tion of the multitudinous all pervasive functions of the liver focuses our attention on the great importance of this organ in the body economy. One can appreciate the extent of its chemical activity by considering that 50% of oxygen in the basal state is consumed in this single organ. The number of functions attributed to the liver (*amounting to about 500*) staggers the imagination but even at that are probably incomplete. An understanding of these functions is essential for the understanding of symptoms and is indispensable for comprehending and evaluating laboratory tests which indicate derangement of these functions.

I

Pigment Metabolism (Bile Secretion and Excretion)

Bile

Bile is secreted continuously by the normal liver and averages about 500 cc per 24 hours *in a normal adult. The rate of secretion is somewhat higher* during waking hours. The discharge into the intestine is intermittent and is controlled by the intake of food and gallbladder function (Chapter 16). The bile secreted by the liver is over 97% water. The solids consist of bile pigments, bile salts, lipids and mineral salts in the approximate concentration noted in Table 1. The total volume and rate of bile secretion is controlled by various factors—neural, humoral and chemical (Table 2).

Table 1

Composition of Human Bile

Constituent	Hepatic Bile	Gallbladder Bile
Water	97.48	83.98
Mucin and pigment	0.53	4.44
Bile salts	0.93	8.70
Fatty acid	0.12	0.85
Cholesterol	0.06	0.87
Lecithin	0.[illegible]2	0.14
Neutral salts	0.83	1.02

From Hammarsten

Bile secretion is under vagal control and therefore electrical or chemical (by cholinergic drugs) stimulation of the vagus results in an increment of bile secreted. On the other hand anticholinergic atropine like drugs may reduce *the secretion. Secretin stimulates bile secre*tion. The bile thus formed has a lower viscosity (Grossman and associates 1949). Bile salts *as well as bile acids are powerful stimuli to bile* secretion; the composition of this bile is similar to that resulting from secretin stimulation. Conjugated bile acids (glycocholic, taurocholic acid) increase the volume as well as the total *solid content of the bile*, while the unconjugated oxidized preparations (dehydrocholic acid) result in an increase in volume but the absolute solid content is decreased (Schmidt et al). Diet has an effect on bile secretion as well as on contraction and emptying of the

Table 2

Choleretic Agents

Vagal stimulation	Bile acids
Cholinergic drugs	Water
Secretin	Proteins
Bile salts	Fats

Choleresis—stimulation of bile secretion

gallbladder Fats and proteins stimulate bile secretion while carbohydrates have an inhibitory effect Starvation inhibits bile secretion Dehydration reduces the volume of all secretions including bile Therefore hydration or increased fluid intake increases bile secretion (Table)

Bilirubin

Bilirubin the pigment of human bile the accumulation of which in the blood and tissues results in jaundice—one of the most spectacular findings and symptoms of liver disease—is formed chiefly outside of the liver but normally is *excreted* entirely by the liver The earlier and now discarded conception that bilirubin is *formed* solely in the liver is based on observations that jaundice develops in geese poisoned by hydrogen arsenide but after hepatectomy jaundice does not occur The absence of jaundice in this experimental setting is now thought to be due to the elimination of a large part of the reticuloendothelial system most of which is situated in the liver in this species In man and other species the reticuloendothelial system outside of the liver is responsible for much or most of the bilirubin formed The extrahepatic formation of bilirubin is proved by the development of jaundice in hepatectomized animals and the intense jaundice in diffuse hepatic necrosis in man

Since the liver contains reticuloendothelial structures some bilirubin is undoubtedly formed by it While the reticuloendothelial cells (Kupffer cells) of the liver are probably responsible for bilirubin formation in this organ there are still some that claim the hepatic cells carry on this function The relative proportion of bilirubin formed intrahepatically and extrahepatically has not been determined but it probably varies in different species and perhaps even in individuals of the same species The occasional patient who dies from diffuse hepatic necrosis without exhibiting icterus may have most of the pigment formed in the liver Another possible explanation however is a suppression of the reticuloendothelial system by the hepatic necrosis

Bile Salts

The bile salts are an integral part of the composition of bile They are the sodium salts of glycocholic and taurocholic acid and are formed from the combination of glycocoll (glycine) and taurine with cholic acid This conjugation of glycocoll and taurine with cholic acid takes place only in the liver hence when the liver is injured the output of bile salts may be decreased by as much as 50% The bile salts are normally reabsorbed in the intestines and re-excreted by the liver so that little new bile salt production is required In extrahepatic biliary obstruction the bile acids may increase in the blood several fold (Friedman and coworkers 1951) over their normal value of 2 5 to 6 0 mg % however in continued post hepatic obstruction sufficient liver injury takes place to reduce bile salt synthesis

Bile salt synthesis is readily impaired even by minor injury The production of a biliary fistula i e the diversion of bile salts from the intestinal tract results in a reduction of bile salt production by the liver It appears that enterohepatic circulation of bile salts is essential for normal hepatic function (Whipple and Smith)

Bile salts are necessary for fat absorption from the intestine Therefore decreased or absent secretion of bile salts into the bowel from either obstruction or liver injury will result in steatorrhea Parenchymatous liver disease may show steatorrhea on this basis even in the absence of jaundice however not all patients with liver disease show this defect (Gross and associates 1950)

Bilirubin Formation

Hemoglobin is the normal source of bilirubin This conversion can apparently be accomplished in vitro by incubation of erythrocytes under sterile conditions Hematin one of the degradation products of hemoglobin is also converted to bilirubin but this reaction takes place more slowly The hemoglobin molecule consists of a protoporphyrin to which the iron is bound and globin the protein fraction Hemoglobin is changed to verdohemoglobin (a green pigment) by opening of one of the

porphyrin rings The iron molecule is easily split off from the verdohemoglobin Up to 5% of circulating hemoglobin and up to 8% of erythrocyte hemoglobin may be in this form The verdohemoglobin is in turn changed to bilirubin iron globin this in turn loses the iron and is changed to bilirubin globin The globin part of this molecule is really an albumin The iron becomes attached to and is transported by the serum globulin (Watson) (See Diagram A)

Total Direct and Indirect Bilirubin

The normal total serum bilirubin concentration may be as high as 1 mg (or even 1 5 mg) per 100 cc It is usually below 0 8 mg % The circulating bilirubin consists of two forms the so called direct and indirect types of bilirubin This distinction is based on the Van den Bergh reaction in the direct type of bilirubin the diazoreagent gives a color reaction without the addition of alcohol whereas the indirect bilirubin gives the color reaction only after treatment with alcohol Their chemical difference is thought to depend on the firmness of the association of the pigment with serum albumin The bilirubin globin (indirect type) is chemically bound to the protein while the direct bilirubin is attached loosely or adsorbed to the albumin Watson mentions that there may be a chemical difference between the direct and indirect types of bilirubin and that mesobilirubin may be responsible for the delayed reaction while bilirubin is responsible for the direct reaction

The nature of and the difference between the two forms of bilirubin described above are not universally accepted According to the recent observations of Najjar the two pigments differ not in their attachment to a protein but in their attachment to a metal Differences in behavior to the diazoreagent as well as other chemical and physical differences were demonstrated in in vitro experiments after removal of the protein It has been suggested that the direct bilirubin is bound to a metal other than sodium and alcohol facilitates the formation of this bilirubin metal complex and thus makes the indirect bilirubin responsive to the diazoreagent In the blood stream the bilirubin is loosely bound to an alpha globulin fraction when this reaches the bile ducts the bilirubin metal complex is formed In bile duct obstruction this bilirubin metal complex regurgitates into the blood stream In the blood stream the bilirubin metal complex may be attached to albumin Najjar s conception about the direct and indirect bilirubin may be presented as follows

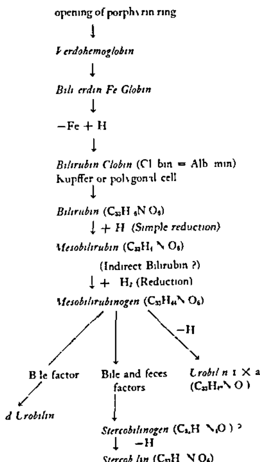
Hemoglobin → Biliverdin globin → Bilirubin globulin (indirect) → Bilirubin metal complex (direct formed in the bile ducts) → Bilirubin metal albumin complex (direct in the serum)

DIAGRAM A SCHEME OF BILE PIGMENT FORMATION

Hemoglobin

Hemoglobin molecule = 4 heme molecules plus 1 globin molecule (M wt 60 000)

Heme molecule (M Wt 600) = protoporphyrin (4 pyrrol ring plus Fe)



Modified from C J Watson New England J Med 2 7 665 194

This formulation is based on sound in vitro observations It is not clear what if any role the liver or Kupffer cells play in this conversion If the liver plays no role in this conversion how can one explain the formation of the direct bilirubin before the pigment reaches the biliary channels i e when the block is in the parenchymal cells? An increase of the direct reacting bilirubin is a sign of regurgitation of pigment after it has passed the Kupffer and perhaps the hepatic cells There is a difference in renal excretion between two forms of bilirubin which is very useful clinically The bilirubin globin (indirect) is not excreted by the kidney while bilirubin direct is readily excreted in the urine

Biliverdin

Biliverdin is a dark green pigment (Table 3) formed by oxidation or dehydrogenation of bilirubin it is found only in regurgitation type of jaundice and then only in small concentrations (1 0 mg %) In extrahepatic biliary tract obstruction due to malignant neoplasms this pigment finds its highest serum elevation This increased biliverdin retention may account for the characteristic green jaundice observed in this group of patients

Urobilinogens

The bilirubin excreted into the gastrointestinal tract is reduced into mesobilirubinogen and stercobilinogen These are two urobilinogens found in the feces and urine They reach the kidneys by absorption from the gut where they are formed part of these absorbed urobilinogens are changed and re excreted by the liver and normally only very small amounts are excreted by the kidneys The site of formation of urobilinogen appears to be the colon (Hollan) therefore the absorption must also

Table 3

Color of Vario s P gments Derived from Hemoglobin

Hem glob n	Red
Hematin	Brown
Protoporphyrin	Red
Verd hemogl b n	Green
B l rubin	Orange (orang red)
Biliverdin	Dark green
Urobilin gens	
M sob l rub ogen	Colorless
Stercob linogen	Colorless
Stercobilin	Orange-yell w

take place in this portion of the intestine That the normal bacterial flora is responsible for this conversion of bilirubin into urobilinogen has been demonstrated by studies on patients receiving antibiotics orally (Robbins Hollan) The administration of aureomycin and Terramycin and probably other antibiotics results in a sharp decrease of fecal urobilinogen during the first 48 to 72 hours of therapy and normal concentrations may not return for six or seven days after discontinuance of these drugs In view of the demonstrated ability of the intestinal bacteria to develop a resistance to and escape from the effect of antibiotics it is probable that with prolonged administration of antibiotics the inhibitory effect on urobilinogen formation would cease in time

Coproporphyrins

The coproporphyrins another group of pigments derived from protoporphyrin are found in both health and disease and are related to hepatic function Coproporphyrin I and III are found in normal individuals Uroporphyrin is normally present in the organism prenatally but later in life its presence in the urine is abnormal Uroporphyrin is derived from coproporphyrin III (Watson and Larson)

2

Clinical Laboratory Tests Involving Bilirubin and Urobilinogen

Total Bilirubin

Estimation of the total bilirubin is a valuable test in the study of hepatic disease. This can be done by determination of the quantity of bilirubin usually by the Malloy-Evelyn procedure or by determining the icteric index. The latter depends entirely on the degree of discoloration of the serum and is not as accurate as the quantitative bilirubin determination. The normal value for the icteric index is 6 to 8 units and for the quantitative bilirubin 1.0 mg. % or less. The rise of these values above normal may be caused by any of the following conditions:

1. damage to hepatic cells
2. obstruction of intrahepatic bile duct
3. obstruction of extrahepatic bile duct or
4. increased production of bilirubin due to increased hemolysis

Direct (Prompt Reacting) and Indirect (Delayed Reacting) Bilirubin

Thus it can be seen that an increased serum bilirubin value is not necessarily indicative of intrinsic hepatic disease. It was suggested that a fractionation of the bilirubin into the direct and indirect types may help to differentiate these forms of jaundice. Cantarow and collaborators (1942) by determining the direct type of bilirubin at the end of 30 minutes found that this fraction is elevated to abnormal levels even in the presence of a normal total bilirubin level and concluded that this determination may help in detection of early hepatic abnormalities. By using this method they found that the normal direct serum bilirubin is 0 to 0.352 mg. % and the relative concentration of the direct bilirubin is 44 to 75% of the total, the larger value being found in individuals with lower total bilirubin.

The conception about the direct and indirect bilirubin has undergone further modification. The terms *prompt direct reacting* or *one minute bilirubin* were introduced. It was proposed that the bilirubin giving not only a direct reaction but also a prompt reaction within one minute was the type that regurgitated from the biliary passages (Ducci and Watson). The delayed but direct reaction obtained at the end of 30 minutes was obtained with a type of bilirubin more akin to the indirect type. It seems that the one minute or prompt reacting bilirubin determination may be useful in the detection of early interference with the excretion of bilirubin.

An analysis of the value of determining the prompt reacting and total serum bilirubin in 279 jaundiced patients has recently been reported by Schaffner and co-workers. They found no correlation between morphological evidence of liver cell damage and the ratio between the prompt reacting and the total bilirubin. This study did not include patients with hemolytic types of jaundice in whom the indirect bilirubin predominates. In general the values for the prompt bilirubin increased as the total bilirubin increased regardless of the cause of the jaundice. As the jaundice became intense the indirect bilirubin increased more rapidly than the prompt reacting type. Toxic hepatitis and extrahepatic biliary obstruction gave the highest ratios of the prompt reacting to total bilirubin (43.48% and 43.45% respectively) as well as the highest total bilirubin. The most significant and constant finding was the increase of this ratio in all the

jaundiced patients as compared with normal individuals

This increase of the prompt reacting bili rubin in a parallel fashion in both patients with parenchymal cell damage and those with extra hepatic obstruction favors the theory that the Kupffer cells and not the parenchymal cells are responsible for the conversion of the de layed to the prompt reacting type This hypothesis is further upheld by the observa tion that as the jaundice increases the in direct bilirubin begins to rise parallel with the direct and the ratio of the prompt to total decreases but not to the level of normal Early in parenchymal cell injury the Kupffer cells efficiently form the prompt bilirubin but the damaged liver cells are unable to excrete it and it returns to the blood stream The bili rubin formed by the Kupffer cells accumulates in these cells since it is not being accepted by the parenchymal cells This accumulation of bilirubin in the Kupffer cells interferes with their function and they cease accepting in direct bilirubin from the blood hence the two fractions begin to rise equally

Klatskin and Drill (1950) question the con cept of the existence of two distinct types of serum bilirubin and attribute little diagnostic value to the prompt and delayed diazoreac tion A recent report from Watson s (Zieve et al) laboratory affirms the usefulness of this test But even in their data there is much over lapping of results especially between hepato cellular (hepatic) and post hepatic (obstruc tive) jaundice (Table 4) The quantitative determination of the two types of bilirubin is decidedly of help in detecting prehepatic (hemolytic) jaundice where only the delayed fraction is increased and in early regurgitation jaundice where there may be a rise only in the direct fraction while the total bilirubin remains the same A prompt reacting bilirubin level of above 0 25 mg % is considered ab normal by Watson It is likewise true that these same deductions may be made from a combina tion of other tests and clinical data (see Differ ential Diagnosis of Jaundice pp 65 71)

Bilirubin Excretion (Clearance) Test

Bilirubin injected intravenously has been used as a test of the functional capacity of the liver One milligram of bilirubin per kilogram of body weight dissolved in a small amount of 0 1 M sodium carbonate is administered in travenously The serum bilirubin is determined before and four hours after its administration A retention of over 5% of the injected bilirubin is considered abnormal This is an extremely sensitive test for liver injury but it has the disadvantages of the costliness and scarcity of purified bilirubin and the test cannot be used in the presence of jaundice To circumvent this last drawback and to make the test more

TABLE 4

Cases Illustrat g Relat onship of B lirub nuria to the One Minute and Tot l B l rubin Values a d to the Bil rubin Rat o

C	D agno	St m B l b		B l b R t (1 /T × 100)	U B l b
		1 M B l rubin	T l B l b		
1	Cirrho s	0 5	0 7	71 4	o
2	Hepatic ci oma t sis	0 5	1 0	50 0	+
3	Hepat tis (without jaund c)	0 8	1 8	44 4	+
4	Hepatit s (sub id ng)	1	6	46	+
5	F mili l hem jaund ce	0 2	3 2	7 5	o
6	Familial hem jaund ce	0 3	3 5	8 6	o
7	Cirrhosis	1 9	4 0	47 5	+
8	F mil l h m jaund ce	0 4	5 2	7 3	o
9	Commo d ct stone	6 4	8 4	76 2	+
10	Carc noma of the pan eas	6 1	8 7	70 1	+
11	C stit tion l he p tic dysf	1 0	8 8	10 9	o
12	F mil l h m j und ce	0 7	9 8	7 2	o
13	F H J a d C D ston s	5	11 0	47 3	+
14	Cirrhosis	5 9	11 4	51 8	+
15	Ac te trophy	5 2	14 7	35 4	c
16	Int til cirrho is	0 6	14 8	4 0	o
17	Common d ct stone	.0 0	9 4	68 0	+
18	C rc noma of the p cr as	17 8	1 8	56 0	+
19	C rci oma f th p nc eas	7 0	44 5	60 7	+
0	Ac te atrophy	31 9	51 2	6 3	+

From Z ve H ll Hanson F lco e and Watson Nor m l d Ab ormal V riat ons and Cl c l S gn fican e of the On M te and Total Se um B lirubi D ter mi at ons J Lab & Cl Med 38 446 1951

sensitive Weech and associates proposed a modification of this test in which the ' velocity constant of excretion is determined from three samples of blood taken before 5 minutes after and four hours after injection of bilirubin

Bilirubinuria

The detection of bilirubin in the urine is a simple bedside procedure which can be helpful in detecting early hepatic dysfunction It is well known that bilirubin appears in the urine before the tissues become icteric This can be verified even grossly by the marked brown discoloration of the urine before icterus of tissues takes place However when the bilirubinuria is not marked chemical means for detecting it have to be utilized It has even been claimed that bilirubin may appear in the urine before or without a rise of the icteric index or the total serum bilirubin This can be attributed to either a decrease of renal threshold or more likely to a rise in the prompt reacting bilirubin to a level where it begins to spill through the kidney without a rise of the total bilirubin

The simple foam test or nitric acid test will detect bilirubin if it is present in considerable amounts Meyers proposed the use of two drops of methylene blue added to 10 cc of urine a brilliant green color is indicative of the presence of bilirubin in the urine Stokes and coworkers were not impressed with the accuracy of this test and thought that the green color was due to a combination of the blue dye with the yellow urine

The Harrison spot test which depends on the formation of a bilirubin barium chloride precipitate and the development of a green color when a drop of Fouchet s reagent is added to the filtered precipitate is a simple as well as useful and reliable test Several modifications have been proposed to make the test more useful and to make it unnecessary to filter the urine Watson and Hawkinson proposed the barium strip modification In this test filter paper is immersed in a saturated solution of barium chloride This is later dried and cut into strips These dry impregnated strips of filter paper are partially immersed in the test urine for 5 to 10 seconds Fouchet s reagent is dropped on the filter paper at the point of contact with the surface of the urine Franklin modified this test by using large plaster of paris tablets impregnated with barium chloride having a concavity on one side The urine tested is dropped into the concavity and allowed to soak in The bilirubin is adsorbed at the surface and the addition of 1 to 2 drops of Fouchet s reagent brings out the green color if bilirubin is present

Urobilinogenuria (24 Hour Quantitative Test)

The determination of urinary urobilinogen is a sensitive indicator of hepatic dysfunction as well as a valuable tool in the differential diagnosis of various types of jaundice The latter problem is discussed in the chapter on Differential Diagnosis of Jaundice The urobilinogen normally reabsorbed from the intestines is promptly excreted by the liver so that only a trace or minute amounts appear in the urine With Watson s procedure the normal 24 hour urinary urobilinogen is usually 0 5 to 1 5 mg occasionally a value of 3 5 mg is noted

The damaged liver is unable to dispose of this chromogen the excess is therefore diverted to the kidneys and the urinary urobilinogen rises Steigmann and Dyniewicz have pointed out a marked discrepancy between the Sparkman and Watson methods of quantitatively determining urinary urobilinogen The Sparkman procedure frequently gives falsely high values because of non urobilinogen chromogens Thus a 24 hour urinary urobilinogen value of over 3 0 mg by Watson s procedure can be considered abnormal and indicative of hepatic dysfunction if hemolysis is ruled out This differentiation is discussed in Chapter 12 However quantitative 24 hour determinations are cumbersome to carry out If the collection of urine is incomplete a false negative (low) result may be arrived at Moreover precaution must be taken to prevent oxidation of urobilinogen to urobilin by storing the urine in a refrigerator in a brown bottle to which is added 5 grams of sodium carbonate and petroleum ether If these precautions are not carried out the urobilin must be reduced to urobilinogen before determination is made

Semiquantitative Urine Urobilinogen Test

A useful semiquantitative bedside procedure for determining urine urobilinogen is that of Wallace and Diamond. One cubic centimeter of Ehrlich's* aldehyde reagent is added to urine diluted 1:10, 1:20, 1:30, etc. The highest dilution that gives a definite pink color is the final one read. The color should develop in five minutes. Normally, only the 1:10 dilution is positive. The higher the dilution that is positive, the greater the concentration of urobilinogen. Because of the ease with which this procedure is carried out, it can be done daily even in the home or physician's office, so that the course of the illness is easily followed. In a patient with early hepatitis urinary urobilinogen increases so that the test is positive in dilutions of over 1:20. As complete intrahepatic obstruction occurs, the urinary urobilinogen may disappear (1:10 or less). Still later, the intrahepatic obstruction decreases, bile enters the intestine, and the urinary urobilinogen goes up to 1:40 or higher. Finally, as the patient gets well, the normal value of 1:10 is again obtained. Fluctuations of the urinary urobilinogen may be followed from day to day with this simple test.

Two Hour Quantitative Urine Urobilinogen Test

Watson and co-workers (1944) proposed a simplified method for evaluating quantitatively the urine urobilinogen, using an Evelyn photoelectric colorimeter or comparator block. To circumvent the inherent problems of 24 hour urine collections, they proposed a quantitative determination on two hour urine samples. Since the highest rate of metabolic activity is in the afternoon, they proposed that the 2 to 4 p.m. sample was the most likely to yield positive results.

Procedure. The patient is instructed to empty the bladder at 2 p.m. and then drink one glass of water. At 4 p.m. the bladder is again completely emptied and this urine is analyzed. Petroleum ether extraction is not done; this therefore introduces a slight error since other chromogens give a color reaction with Ehrlich's reagent. However, since these are small quantitatively and increase parallel with urobilinogen, the results are not invalidated for clinical purposes.

They report their results in Ehrlich units rather than milligrams of urobilinogen, since other substances besides urobilinogen are determined. Four Ehrlich units are equivalent to 1 mg. in terms of urobilinogen. In 90% of their normal controls, the 2 hour sample gave values of less than 1 unit, while patients who had liver disease or other disease that would tend to impair liver function showed values above 1 unit. In a case of hepatitis the value was more than 12 units. In about 15% of cases this test disagrees with the quantitative test (Voegtlin and co-workers).

UROBILINOGEN TOLERANCE TESTS

Since an impaired liver is unable to excrete the urobilinogen that reaches it, an attempt to use a loading test to overburden this excretory power of the liver is a rational approach. Watson in 1936 administered 50 mg. of urobilin intramuscularly or intravenously to normal individuals and to patients with jaundice. The urobilin was reduced to urobilinogen in the normal individuals; only a small amount was excreted by the kidneys (2-5 mg./24 hours), while a marked rise occurred in patients with cirrhosis (up to 32 mg.), as well as those with common duct obstruction and those with jaundice resulting from mapharsen therapy.

With (1946) also used a urobilinogen tolerance test in normal individuals and patients with liver disease, but he used smaller amounts of urobilinogen. He injected 10 mg. intravenously in subjects whose urinary excretion of this pigment was below 1 mg. per 24 hours, but more in those who excreted 3 mg. per 24 hours. He concluded that a damaged liver is unable to excrete urobilinogen, since most of the patients with hepatitis showed a marked rise in urinary excretion. However, most of these patients showed slight icterus. He pointed out that in patients with portal hypertension and collateral circulation the decrease in hepatic excretion may be due to shunting of some of the material away from the liver.

Mann and Koler administered urobilinogen

* Ehrlich's reagent: 0.7 gm. of p-dimethylaminobenzaldehyde, 150 cc. of concentrated HCl, 100 cc. of H_2O.

intravenously to normal rats with biliary fistulas and were impressed with the remarkable capacity of the normal liver to excrete this compound When administered by this route 75% of the injected material promptly appeared in the bile and a much smaller fraction in the urine Subcutaneous administration resulted in the excretion of 50 to 70% in the bile in eight hours and 4 to 25% in urine This considerable excretion in the urine in presumably normal animals demonstrates that even the normal mechanism may be overburdened however animals with bile fistulas may not be presumed to be normal They also demonstrated that orally administered urobilinogen is absorbed but poorly under the conditions of these experiments

Urinary Coproporphyrins

Normal

Coproporphyrins are also derived from the protoporphyrin fraction of the hemoglobin molecule The I and III isomers are found in normal persons These vary somewhat according to age In the young 16 to 89% of coproporphyrin I is excreted in 24 hours 1 4 to 31 7% of coproporphyrin III is excreted in that period In older persons these values are 14 7 to 57% and 4 5 to 34 3% respectively Although there is a variation in excretion in normal individuals the total daily urinary coproporphyrin is under 100 The type III isomer is normally 40% or less of the total

Abnormal

The urinary coproporphyrins are increased in mechanical biliary obstruction and in hepatocellular jaundice however the persistence of increased urinary coproporphyrin after disappearance of jaundice points toward hepatocellular damage It is interesting to note that coproporphyrin I is increased in infectious hepatitis while type III is increased in cirrhosis and chronic alcoholism The highest values are reached in cirrhosis and hepatitis probably because in these conditions there is a combination of hepatocellular damage and intrahepatic biliary obstruction The increase of urinary coproporphyrins is apparently a sensitive index of hepatic dysfunction (Watson and co workers 1951) since it occurs even in the absence of jaundice and in the presence of normal urine urobilinogens However because of its technical complexity the test has not become useful in the clinical laboratory In the presence of frank icterus it would be of limited value in differential diagnosis since it rises in both the hepatic and the post hepatic type of jaundice

3

Excretory Function of the Liver

BESIDES the normal constituents of the bile—sodium bilirubinate bile salts fatty acids cholesterol and lecithin—the liver excretes other substances This excretory power may be part of its detoxifying functions It excretes bacteria such as the typhoid bacillus chemotherapeutic agents sulfonamides antibiotics e g aureomycin terramycin and streptomycin as well as various other drugs and heavy metals This excretory function is utilized clinically in the dye clearance tests

Phenoltetrachlorphthalein

The use of various dyes that are excreted by the liver to test the functional integrity of the liver probably dates back to the introduction

of phenoltetrachlorphthalein for this purpose by Rowntree and co workers in 1913 originally the amount of dye excreted was determined by analysis of stools This unsatisfactory procedure was later modified by recovery of dye by duodenal intubation Finally its disappearance from the blood was proposed as the most satisfactory indication of hepatic functional integrity (Rosenthal 1922)

Rose Bengal and Azorubin S

Other dyes that have been previously used in liver function tests and that have generally been discarded are rose bengal (diiodotetrachlorfluorescein) and azorubin S Greene in his recent review of liver function tests cites a comprehensive bibliography of these as well as other tests

The rose bengal test is performed as follows

1. Ten cubic centimeters of a 1% solution of dye (diiodotetrachlorfluorescein) is injected intravenously
2. A sample of blood is withdrawn after two *minutes* for dye determination This is considered the 100% reading
3. An eight *minute and sixteen minute* sample of blood is withdrawn and analyzed by means of a spectrograph

Normal values are considered to be 55% and 35% or below in the eight and sixteen minute samples respectively Monroe and Hopper recently compared the rose bengal test as determined by the visual spectrograph with the Bromsulphalein test and found the latter more sensitive

The azorubin S test requires duodenal intubation and recovery of the dye in the biliary drainage Four cubic centimeters of a 1% solution of the dye is injected intravenously Duodenal aspirates are checked every 1 to 2 minutes for the cherry red color of the dye Normally the dye appears in the duodenum in 17 to 29 minutes delayed appearance signifies hepatic dysfunction Rosenberg and Soskin found this test comparable in accuracy with the Bromsulphalein (BSP) test but the need of duodenal intubation makes it cumbersome and impractical

Sulfobromophthalein Sodium (Bromsulphalein BSP) Test

The sulfobromophthalein sodium (Bromsu phalein BSP) excretion test is the most prac cal and most commonly used of the dye tests well as one of the most practical tests of liv function It was introduced by Rosenthal a White in 1925 Originally the recommend dosage of dye was 2 mg per kilogram of bo weight but this has been changed to 5 mg p kilogram with resultant increase in sensitiv of the test The technique most commor used and the one which I think is most adap able *to clinical practice consists of inj cti* 5 mg of dye per kilogram of body weight a withdrawing a sample of blood 45 minu later for determination of the percentage the dye retained The dye is put up by t manufacturer in 3 cc sealed ampules contain 50 mg of dye per cubic centimeter Thus 60-kilogram individual would require 6 c or 300 mg (the contents of two ampule

The necessary dose can be injected quic (1 to 2 minutes) intravenously without u *toward effect It is preferable that the patie* be in the recumbent position to avoid synco and to avoid extravascular infiltration T latter may produce a painful swelling whi disappears readily after local application heat The 45 minute sample should be obtain from the opposite arm to avoid picking minute amounts of the dye that may ha been absorbed by the tissues locally [syringe should be dry and clean to preve *hemolysis of the erythrocyte The blood* allowed to clot and the supernatant serum removed after centrifugation The blue co of the dye is brought out by alk*alinization* w sodium hydroxide and the amount of dye in t sample is determined by photoelectric colori eter or by comparison with a standard d solution

Interpretation

The amount of dye retained at the end 45 minutes determines the presence and t degree of hepatic dysfunction Usually there no dye retained at the end of 45 minutes normal subjects however a *retention of* to 4% can be considered within normal limi In addition to its ease of performance this t

is one of the most sensitive available It is frequently positive in mild early cirrhosis when other tests are negative For this reason it has been proposed as a screening test for patients who are admitted with upper gastro intestinal hemorrhage to differentiate hemor rhage from esophageal varices (cirrhosis) and from bleeding peptic ulcer (Zamcheck 1950) It becomes positive in malignant tumors with metastases to the liver and in this respect can be used preoperatively and postoperatively as a prognostic aid

One of its chief drawbacks is its lesser useful ness in the presence of jaundice Icteric serum interferes with color comparison however this can be circumvented by using the patient s serum prior to dye injection as the blank The chief drawback against using this test in the presence of jaundice is not technical but a question of interpretation

TABLE 5

Table of Values to be Subtracted from Bromsulphalein Test Result Corresponding to Various Levels of One Minute Bilirubin

One minute bilirubin	0 0	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9
1	0	1	2	3	4	5	6	6	7	8
2	8	9	10	10	11	11	1	12	1	13
3	13	14	14	14	15	15	15	16	16	16
4	17	17	17	18	18	18	18	19	19	19
5	19	0	20	20	0	21	21	21	21	21
6		2	2	22	22	23	3	3	3	3
7	3	4	4	4	-4	4	4	25	5	25
8	5	25	5	6	6	26	26	6	6	26
9	7	7	7	7	27	27	7	7	28	28
10	8	28	28	8	28	28	8	9	29	29
11	9	9	29	9	9	9	30	30	30	30
1	30	30	30	30	30	30	31	31	31	31
13	31	31	31	31	31	31	31	32	32	32
14	32	32	32	32	3	32	32	3	33	33
15	33	33	33	33	33	33	33	33	33	33
16	33	34	34	34	34	34	34	34	34	34
17	34	34	34	34	34	35	35	35	35	35
18	35	35	35	35	35	35	35	35	35	35
19	36	36	36	36	36	36	36	36	36	36
0	36	36	36	36	36	36	37	37	37	37
21	37	37	37	37	37	37	37	37	37	37
2	37	37	37	37	38	38	38	38	38	38
23	38	38	38	38	38	38	38	38	38	38
24	38	38	38	39	39	39	39	39	39	39

From Zieve Hanson and Hill Studies of Liver Function Tests II Derivation of a Correction Allowing Use of the Bromsulphalein Test in Jaundiced Patients J Lab & Clin Med *37* No *1* 40–51 Jan 1951

The question arises Is the dye retention in the blood due to inability of the liver cells to excrete it (the function we are trying to measure) or is it due to regurgitation from the obstructed bile ducts? And if both mecha nisms are responsible for the dye retention what is the relative influence of each factor?

Interpretation in the Presence of Jaundice

Zieve and co workers attempted to answer these questions by using the Bromsulphalein test and determining total and one minute bilirubin in 94 patients with jaundice of various types they analyzed the resultant data mathe matically They concluded that in a patient with a one minute bilirubin of less than 1 mg % and total bilirubin of less than 2 mg % the Bromsulphalein retention varies independ ently of the serum bilirubin and is there fore valid in itself while with higher values for serum bilirubin there is a tendency for a parallel increase in the bilirubin and Bromsul phalein retention Therefore in cases with progressively increasing jaundice the Bromsul phalein retention is progressively more de pendent upon factors of regurgitation They present a mathematical formula from which is derived a table and a graph for correcting the Bromsulphalein retained in the serum for the factor of regurgitation

Thus for example if a patient has a one minute bilirubin value of 14 and Bromsul phalein retention of 57% (see Table 5) for this level of bilirubin the Bromsulphalein regurgitation is 32% The 32% is subtracted from 57% giving the corrected value of 25% as due to retention and therefore liver dys function (Table 5)

The corrected values for the Bromsulphalein retention correlated well with the results of the other hepatic function tests and patho logical findings If this formula proves to be correct upon further study it will make this test as important in icteric patients as it is at present in anicteric subjects

Giges has pointed out that in the presence of jaundice BSP may remain in the serum for days after its administration In patients with hepatitis with considerable icterus the dye remained in the blood 2 to 1- days The length

of retention did not correlate too well with the hyperbilirubinemia Thus in a patient with a serum bilirubin level of over 25 mg % there was a six day retention while the longest retention (12 days) occurred in a patient with a serum bilirubin level of 18 8 mg %

Method of Removal of BSP by the Liver

Since the Bromsulphalein test is accepted as an excellent indicator of hepatic function it may be tacitly assumed that removal of the dye from the blood stream and its excretion into the biliary passages *is entirely* dependent on the polygonal cells of the liver While the preponderance of evidence probably favors this view there is some difference of opinion about the importance of the Kupffer cells in this process Wirts and Cantarow are of the opinion that the Kupffer cells remove the dye from the blood stream and the polygonal cells excrete it Others are of the opinion that the reticuloendothelial system is responsible for removal of the dye from the blood (Klein and Levinson Mills and Dragstedt) The interference of India ink with excretion of BSP has been attributed to its effect on the Kupffer cells however it has been shown that India ink interferes with parenchymal cell function and this perhaps by virtue of sinusoidal obstruction (Mendeloff and associates) Bromsulphalein has been shown to become localized in the parenchymal cells by the use of radioactive dye (containing S^{35}) There is therefore an abundance of experimental evidence to support the clinical assumption that BSP clearance measures the functional integrity of the parenchymal cells of the liver

Influence of Other Factors on Bromsulphalein Clearance

Circulatory factors The influence of other factors—both hepatic and extrahepatic—and other substances on the removal of BSP from the serum are of more than passing interest to the clinician and have been abundantly discussed in the literature Ingelfinger and his group have been so impressed with the capacity of the liver to remove the dye from the blood that they utilized it for estimating hepatic blood flow (EHBF) They found the normal percentage disappearance rate (PDR) from the serum to be from 10 to 16% per minute and to depend on hepatic cell function and hepatic blood flow The PDR is very low in patients with cirrhosis and congestive heart disease The effect of circulatory failure in impairing Bromsulphalein excretion has been alluded to on the basis of clinical observations (Blumberg and Schloss)

Extrahepatic removal of BSP Cohn and co-workers have shown in eviscerated hepatectomized and nephrectomized animals that the *extrahepatic tissues* do remove BSP At the end of 70 minutes 50% of the injected dye had disappeared from circulation However in the intact animal the removal of BSP by other tissues is negligible as compared with that removed by the liver

Ingestion of food Ingestion of food has been found to have no influence on BSP clearance by some (Ingelfinger and co workers) and to improve dye removal by others (Havens and associates) Exercise apparently decreases the PDR perhaps by decreasing hepatic blood flow Cantarow and collaborators suggest that bilirubin and BSP compete for the same excretory mechanism but that BSP receives preferential treatment Rose bengal and fluorescein did not appear to interfere with BSP excretion but BSP interfered with rose bengal excretion Injection of two doses of the dye (BSP) in rapid succession would overload or saturate the excretory mechanism and result in decreased removal of dye Sodium dehydrocholate injected intravenously can cause transient but complete inhibition of BSP removal The simultaneous performance of BSP hippuric acid and galactose tolerance tests is feasible and gives reproducible results These tests apparently do not interfere with each other and do not overburden the functional capacity of either the normal or the abnormal liver

Renal excretion of BSP Excretion of BSP by the kidneys is negligible in normal individuals amounting to about 1% of the dye injected However in increased dye retention due to hepatic dysfunction the kidneys attempt to rid the body of the dye and renal excretion

increases considerably (Norcross and associates 1951)

Modifications of the Bromsulphalein tests The simple BSP test using 5 mg of dye per kilogram of body weight and taking one 45 minute specimen is so useful clinically that one is hardly justified in discussing at length all the modifications used and proposed Most of the modifications are refinements that increase its accuracy or scope and are designed chiefly for experimental purposes Keeton s group (Lavers and co workers 1949) used serial analysis of the blood at frequent intervals and recorded the blood clearance of dye graphically The shape of the graph and the rate of disappearance (clearance coefficient) of the dye is a more sensitive index of liver dysfunction than a simple 45 minute determination More frequent sampling of the blood for residual dye was proposed but was abandoned because of the increased complexity of the procedure Moses and his group proposed the use of a 15 minute determination and suggested that a value above 25% is abnormal at that time Lorber and Shay s (1952) study of the enterohepatic circulation of Bromsulphalein gives a rational reason for testing the blood level for the dye at shorter intervals According to this study at 45 minutes or 60 minutes considerable Bromsulphalein may be reabsorbed from the gastrointestinal tract and the blood level at that time represents reabsorbed rather than nonexcreted dye

Culbertson and co workers proposed the Bromsulphalein clearance (C_{BSP}) rate as a test of hepatic function They infused the dye at the constant rate of 2 5 mg per minute per square meter of body surface Twelve normal subjects showed a basal clearance of 503 to 1055 cc with an average of 676 cc per minute Two patients with portal cirrhosis showed a clearance of only 384 and 160 cc per minute Several patients with primarily nonhepatic disease showed decreased clearance rates, decreased clearance was also induced by venous congestion of the lower extremity and intravenous injection of epinephrine

Toxic Reactions

Bromsulphalein is remarkable for the rarity with which it produces toxic reactions I have observed loss of consciousness and a mild generalized convulsive seizure in one patient immediately after BSP administration The patient regained consciousness and recovered without any untoward results Chambers and Moister reported a severe reaction in one patient with loss of consciousness and complete apnea This patient had an allergic history Local thrombophlebitis has been observed but is not of a serious nature (Stampien and Rosenquist) Morey and associates observed local allergic skin reactions in two patients and a severe systemic anaphylactoid reaction in another patient after repeated use of BSP they cautioned that its repeated use may result in sensitization Another severe reaction was reported by Andino and McKeown The rarity of the toxic reactions emphasize the safety of this preparation but, because toxic reactions of perhaps allergic nature have been reported it should be used with caution in patients with a strong allergic history and the injection time should be increased from one to three or four minutes

4

Detoxification and Conjugation

THE liver's vast chemical activity includes (1) modification of various substances both endogenous and exogenous and (2) excreting them with the bile into the intestines or returning them to the blood stream and allowing the kidneys to excrete them. Since many of these substances are toxic and the toxic properties are decreased after alteration by the liver, this process is referred to loosely as detoxification. Such teleological inference is unjustifiable since occasionally the altered product is more toxic to the organism than is the original. A splendid example of this is acetylation of sulfonamides which is carried out by the liver. The free sulfonamides are freely excreted by the kidneys without harm to the organism, while the acetylated sulfonamides are poorly soluble in an acid urine, are precipitated in the kidneys and renal pelvis and subject the organism to the harmful effect of renal calculi.

Endogenous Toxic Substances

Conjugation is therefore a more appropriate term for this function of the liver. Fortunately the conjugated compounds are usually less toxic, and this chemical transformation is beneficial in most instances. Thus indole, skatole and phenol are absorbed from the gastrointestinal tract and are rendered less toxic by conjugation with sulfuric acid and potassium or glycuronic acid. Glycuronate formation is an especially common conjugating mechanism. Other toxic substances absorbed from the intestines after their formation by bacterial fermentation are ethylamine, tyramine and histamine. The liver probably plays an important role in their detoxification.

Drugs and Exogenous Toxins

The liver plays a leading role in the detoxification and/or excretion of many drugs and exogenous toxins. The short acting barbiturates are destroyed in the liver by side chain oxidation. Among these are pentobarbital and Evipal. While phenobarbital is mostly excreted by the kidneys, destruction in the liver is also an important mechanism of clearance. These barbiturates should be administered with great caution or not at all in the presence of liver damage. For while they are not directly damaging to the liver, prolonged narcosis and coma may result from their accumulation and persistence in the body. Barbital is almost completely excreted by the kidney; in general barbiturates with short alkyl radicals are eliminated from the body in this manner. It is interesting to note that the short acting barbiturates owe their brief pharmacological life to the efficient hepatic destruction, while the long acting barbiturates owe their longevity to the slow renal excretion.

The liver plays a vital role in detoxification of narcotic drugs. Morphine and the other opiates are detoxified in the liver, and therefore their use should be avoided in severe liver dysfunction. Methadone and meperidine hydrochloride (demerol) are chiefly destroyed by the liver. That this organ plays an important role in the detoxification of tetraethylthiuram disulfide (Antabuse) is evident from studies on partially hepatectomized rats (Boyd and Kirgsmill 1951). This raises the question of the danger of the use of this drug in alcoholics with possible liver damage.

Tests Depending on Conjugation

Hippuric Acid Synthesis

The hippuric acid test introduced by Quick in 1933 tests the conjugating function of the liver. It depends on the conversion of benzoic acid into hippuric acid by conjugation with glycine.

Benzoic acid + glycine = hippuric acid

The test is performed by the oral or intravenous route depending upon the mode of administration of the benzoic acid In both instances the urinary excretion of hippuric acid is determined

Oral Test

The oral test is performed by administration of 6 gm of sodium benzoate dissolved in 30 cc of water This may be flavored with oil of peppermint The patient should be instructed to drink a glass of water after ingestion of the sodium benzoate The optimum time to perform the test is one hour after breakfast The patient voids before the test is begun This urine specimen is discarded and hourly urines are collected and saved for four hours This total collection of urine is analyzed for the quantity of hippuric acid The figure in grams of the hippuric acid is multiplied by 0 68 to obtain the quantity of benzoic acid excreted Hippuric acid $\times$ 0 68 = benzoic acid The average normal excretion of benzoic acid in the oral test is 3 gm in the four hour period but 90 and 120% are considered the lower and upper normal limits

Intravenous Test

The intravenous test is performed by injecting 1 77 gm of sodium benzoate dissolved in 20 cc of distilled water The injection should be given slowly in three to five minutes and preferably one hour after a light breakfast This amount of sodium benzoate is equivalent to 1 5 gm of benzoic acid The urinary bladder should be emptied at the beginning of the test and one glass of water should be drunk to facilitate urination after one hour The complete urine specimen is tested quantitatively for hippuric acid The minimum normal one hour output of hippuric acid is 1 gm or 0 7 gm of benzoic acid

The intravenous test which I prefer has advantages over the oral test It is more accurate because the irregularities and uncertainties of absorption do not play a role Nausea and vomiting after the oral administration of sodium benzoate make the results uncertain or invalid Since only one urine collection is required it is time saving both to the patient and to laboratory personnel

In addition to its technical drawbacks it has certain defects as a liver function test Glycine is necessary for the synthesis of hippuric acid the liver can synthesize this amino acid but if the individual is protein deficient glycine synthesis and in turn hippuric acid synthesis will be impaired Yet this low hippuric acid synthesis will not be dependent on liver disease but rather on protein starvation

As a liver function test it has another defect in that it partly depends on the intactness of another organ If there is renal impairment this may interfere with excretion of the hippuric acid which may have been formed in adequate quantity by the liver Finally the liver is not the only organ that forms hippuric acid from benzoic acid the kidney is also capable of this task Thus the kidney may conceivably compensate for hepatic deficiency and may produce a normal test or because of its impairment may produce a falsely abnormal test

While the hippuric acid synthesis test is useful it has the technical and physiological drawbacks discussed and these impair its accuracy and reliability Other tests are, therefore more commonly used to assay impairment of the hepatic cells Another phenomenon has been observed which has resulted in some confusion of interpretation Rosenberg and Soskin have pointed out occasional *hyperexcretion of hippuric acid* they interpreted this abnormally high synthesis as a sign of mild liver injury with mild irritative hyperfunction More recently Persky and co workers reported increased excretion of hippuric acid in patients with free anxiety while others have shown that patients with catatonic schizophrenia excrete abnormally low amounts of benzoic acid Both of these findings were interpreted as indicating hepatic dysfunction While this conclusion may be correct it may mean simply that the hippuric acid synthesis test measures functions other than those residing in the liver

Para Aminohippuric Acid Synthesis Test

Deis and Cohen proposed the conversion of para aminobenzoic (PAB) acid into para aminohippuric (PAH) acid as a test of hepatic function The test is performed by the ad

ministration of 3 gm of sodium PAB in tablet form orally two hours after a light breakfast Blood determinations of PAB and PAH were made at regular intervals but the one hour serum specimen appears to give the desired information The mean synthesis in 60 normal subjects was taken as 100% patients with liver disea e showed a mean decrease of 30% below normal The test was highly abnormal in patients with infectious mononucleosis but only slightly below normal in those with ob structive jaundice This suggests that the test can be useful in differential diagnosi of jaundice

This te t has an advantage over the hippuric acid test inasmuch as renal excretion is not relied upon The possible deficiency of glycine was eliminated by simultaneous administra tion of 5 gm of glycine It is interesting that they found a high (170% and 140%) synthesis of PAH in two patients with anxiety state

Benzoyl Glucuronate Excretion Test

Another test based upon the conjugating functions of the liver has been proposed by Snapper and Saltzman The liver is capable of using alternating conjugating processes to rid the body of a noxious substance Thus normally the liver conjugates benzoic acid with glycine and excretes it as hippuric acid When the liver is injured and this synthesis is im paired it excretes benzoic acid as the glucuron ate It appears that only the damaged liver uses this alternating conjugation The presence of benzoyl glucuronate in the urine after benzoic acid administration is a sign of hepatic im pairment

The test is performed by administering 5 gm of benzoic acid or 5 8 gm of sodium ben zoate in gelatin capsules Breakfast is omitted lunch is allowed but fruits and fruit juices are eliminated Urine is collected at 4 and 6 hours after ingestion of the benzoic acid The entire specimens are saved in the refrigerator The pre ence of glucuronate is determined by either a qualitative or a quantitative procedure by using naphthoresorcinol solution * The qualitative test is the only one necessary since normally no glucuronate is excreted Glucuronate excretion may be present even when the hippuric acid excretion is normal and indicates hepatic abnormality Snapper claims that it is a very sensitive test of hepatic injury and yet does not become positive in prolonged extrahepatic biliary obstruction It has not been widely used most laboratories are not equipped to perform it therefore at present it must be regarded as an experimental procedure

Methylation of Nicotinamide

Methylation is one of the functions of the liver as demonstrated in both in vivo and in vitro experiments This function is probably exclusively possessed by the liver since neither the kidney nor muscle is capable of carrying out this function Nicotinic acid and nicotin amide are excreted in the urine as methylated compounds (designated as F_2) These methyl ated compounds give off a bluish fluorescence in ultraviolet light when treated with alkali and butinal Testing of the urine for this sub stance has been utilized as a test for nicotinic acid deficiency

Najjar and co workers proposed a nicotinic acid loading test to determine the methylating capacity of the liver They administered a test dose of 50 mg of nicotinamide orally or o mg intravenously and determined the amount of methylated compound excreted in the urine in a four hour period They found that the intravenous and oral tests gave parallel results and that patients with liver disease (catarrhal jaundice and glycogen disease) gave a much lower percentage of methylation than those with nonhepatic diseases This test is more of experimental than of clinical interest

F r t ch ical deta l of the te t see papers b Sn ppe nd Saltzm n

5

Carbohydrate Metabolism

CARBOHYDRATE is an essential fuel for the various metabolic activities of the mammalian organism While fat is also used as a fuel it cannot for long replace carbohydrates as a source of energy The liver maintains a central position in the storage and proper distribution of this essential foodstuff Starches are changed into monosaccharides before absorption Absorption occurs by two mechanisms (1) phosphorylation of the monosaccharide and (2) diffusion Glucose fructose and galactose are absorbed by both mechanisms

The monosaccharides reach the liver via the portal vein and there the nonglucose monosaccharides are transformed into glucose Most of the absorbed glucose is polymerized into glycogen and stored as such and some of it is allowed to proceed into the blood stream to maintain the level of blood sugar The stored glycogen is in turn gradually broken down into glucose to maintain the blood sugar and supply glucose to other organs The formation of glycogen glycogenesis and its breakdown glycogenolysis or glyconeogenesis is a reversible process implemented through a complex system of enzymes This process is carried out by the aid of the phosphate radical The breakdown of glycogen into glucose is referred to as phosphorolysis (analogous to hydrolysis) The better known enzyme which is involved in the phosphorolysis of glycogen (glycogenolysis) is glycogen phosphorylase This enzyme can under certain circumstances reverse the process and aid glycogenesis The direction that this process takes is dependent among other things on the concentration of glucose 1 phosphate and inorganic phosphate An excess of inorganic phosphate accelerates glycogen breakdown On the other hand adenosine triphosphate (ATP) and hexokinase favor glycogenesis

Glycogen storage in the liver not only is important for the maintenance of a normal blood sugar and as a source of glucose for other organs in the body but is essential for the liver Like other organs it needs carbohydrates for its own fuel needs and has a protein sparing effect In a glycogen depleted liver essential proteins may be broken down for ordinary metabolic needs This is equivalent to using the wooden framework of the house to stoke a furnace in the absence of coal The liver also uses glucose for its detoxifying functions by conjugating toxic substances into glucuronates Thus, by their protein sparing action and their aid in detoxification carbohydrates have a protective effect on the liver

In addition to its conversion of other hexoses into glucose the liver also converts amino acids and the glycerin part of fat into glucose The importance of the liver in carbohydrate metabolism can be readily appreciated from the foregoing resume for more details the reader is referred to the excellent monograph on Carbohydrate Metabolism by Soskin and Levine

TESTS DEPENDING ON CARBOHYDRATE FUNCTIONS OF THE LIVER

Several of the carbohydrate functions of the liver are utilized clinically to ascertain its normality The tests in this category are (1) glucose tolerance test (2) adrenalin hyperglycemia test (3) insulin tolerance test (4) galactose tolerance test (5) levulose tolerance test (6) lactate clearance test and (7) pyruvic acid elevation

1 *Intravenous Glucose Tolerance Test*

The liver is essential in the maintenance of a normal blood sugar Thus if the blood sugar level falls the liver breaks down glycogen and discharges glucose into the blood Likewise,

if the blood sugar is raised above normal the liver hastens to remove the excess glucose and deposits it as glycogen The hepatectomized animal is completely unable to regulate to the level of blood sugar The damaged liver likewise may exhibit defects in maintaining a normal blood sugar or removing glucose from the blood at a normal rate In severe liver disease hyperglycemia (and glycosuria) may be noted as well as hypoglycemia the former being a sign of the inability of the liver to remove glucose from the blood and store it as glycogen while the latter is a sign of absence of glycogen in the liver or the inability to break it down (see Glycogen Storage Disease)

Soskin proposed the use of an intravenous glucose tolerance test as a means of testing this function of the liver Oral glucose tolerance tests are not so reliable because of many variable factors such as rate of gastric emptying rate of intestinal absorption and motility The intravenous route eliminates all these variables The test is performed in the fasting state by injecting intravenously 0.33 gm of glucose per kilogram of body weight Blood is obtained for glucose determination before glucose is administered and 30 60 90 and 120 minutes later The normal liver returns the blood sugar to the fasting level within 60 minutes When there is liver impairment this organ is unable to remove the sugar from the blood rapidly enough and then the fasting level may not be attained for 90 or 120 minutes The maximum level of blood sugar attained is of no importance in interpretation of the test The one hour value is the dividing line between normality and abnormality

In pancreatic diabetes mellitus this test like other types of glucose tolerance tests is abnormal However in this disease the blood sugar remains elevated for longer than two hours and not only is the fasting level not reached but the blood sugar remains abnormally elevated (above 1 0 mg %) Confusion may arise between a very mild diabetes and severe hepatic dysfunction To resolve this problem it is advisable to double the dose of glucose to 0.66 gm per kilogram This larger dose should increase the abnormality in case of diabetes mellitus and reduce the abnormality in hepatic dysfunction In the latter situation the higher blood sugar level attained would serve as a stronger stimulus to the liver and glycogenesis would be accelerated It is also well to keep in mind that glucose tolerance tests may show variations dependent upon the previous diet of the patient For this reason the patient should be maintained on a high carbohydrate diet before the test is performed This type of diet is usually adhered to by a patient with suspected liver disease

I have used this intravenous glucose tolerance in patients with hepatitis and cirrhosis and found it to be a sensitive test of hepatic dysfunction well correlated with other liver function tests such as the hippuric acid and Bromsulphalein tests It has the advantage of being a physiological test The disadvantages are technical since it requires numerous vein punctures Moyers and Womack prefer the oral glucose tolerance test and claim that it is more accurate than the intravenous test This is not my experience and because of the variable gastrointestinal factors in the oral test it is difficult to see how it could be superior to the intravenous test

Adrenalin Hyperglycemia Test (*Glycogen Storage or Gluconeogenesis Test*)

Rationale Various endocrine glands influence carbohydrate metabolism and blood sugar levels Among these are the pituitary the thyroid and the adrenals It was noted at the turn of this century that adrenalin injection produces hyperglycemia This hyperglycemia is due to stimulation of hepatic gluconeogenesis since it did not occur in the hepatectomized animal or when the hepatic artery was ligated

Method Adrenalin induced hyperglycemia was suggested as a liver function test by Loeper and Verpy in 1917 but was later discarded as unreliable Recently Kinsell and co workers reintroduced it with modifications as a reliable indicator of hepatic dysfunction The test is performed as follows

1 After a three day period on an adequate carbohydrate diet
2 A fasting blood glucose determination is done
3 Adrenalin 1 1000 is administered intra

muscularly in the dosage of 0 01 cc per kilogram of body weight

4 Blood specimens for glucose determination are obtained at 15 30 45 60 90 and 120 minutes

In a normal individual this curve is similar to a normal glucose tolerance test Since this test seeks to determine the maximum rise of blood sugar or maximum glycogenoly is and since this usually occurs between the 30 and 60 minute period the test can be abbreviated by obtaining blood specimens at 0 30 45 and 60 minutes

In the studies by Kinsell and his group the normal maximum rise of blood sugar ranged between 40 and 100 mg % with an average of 58 mg Patients with mild hepatitis showed a maximum blood sugar rise of 46 mg those with moderately severe hepatitis 32 mg and severe hepatitis 18 mg % Patients with cirrhosis showed responses varying from low to normal values The correlation of this test *with the more commonly* used *liver function* tests are in the neighborhood of 60% (Table 6) These authors refer to this as a test of glycogen storage but it actually tests the ability of the liver to break down glycogen and is of special usefulness in glycogen storage disease (see Chapter 75)

3 *Insulin Tolerance Test*

The importance of the liver in carbohydrate metabolism has induced Waife and co-workers to utilize the insulin tolerance test in patients with liver disease This may test not only the carbohydrate activity of the liver but also its insulin inactivating function since it has been shown that the liver inactivates insulin

TABLE 6

Correlation Between Adrenalin Hyperglycemia Test and Other Liver Function Tests

L F d T st	*C l l*	*C l l*	*Ob rv d*
Cephalin cholesterol flocculation	63%	37%	140
Bromsulphalein retention	61%	39%	13
Thymol turbidity	60%	40%	78
Icterus index	66%	34%	101

From Kinsell Michaels Weiss and Barton Am J M Sc 11 554 1949

Procedure The test is performed by injecting intravenously 0 1 unit of regular insulin per kilogram of body weight Blood sugar determinations are done before the insulin is given every 15 minutes for one hour and at 1½ and 2 hours

Interpretation Normally the blood sugar falls to about 50% of the fasting level in the first half hour and returns to normal within 1½ to 2 hours Patients with cirrhosis showed a lesser degree of hypoglycemia but a marked delay in return of the blood sugar to the fasting level so that while the hypoglycemia was not so marked it was greatly prolonged

This peculiar response to insulin of patients with liver disease is not readily explainable A normal subject who fasted for 40 hours showed *a similar response suggesting that a patient* with hepatic disease responds like a starving individual The prolonged hypoglycemia effect may suggest a defect in inactivation of the insulin The sluggish initial response cannot be *explained on the basis of failure of the damaged* liver to store glycogen upon stimulation with insulin since in the presence of a normal amount of insulin (intact pancreas) insulin injection induces storage of muscle glycogen rather than hepatic glycogen (Soskin and Levine) The test is interesting in its physiological implications rather than its clinical usefulness

4 *Galactose Tolerance Test*

This test attempts to utilize the ability of the liver to convert galactose into glucose

Oral Test This original and now largely discarded procedure consisted of the administration of 40 gm of galactose by mouth and the determination of the urinary galactose excretion in four hours An excretion of 3 gm or less was considered normal while over 3 gm was considered abnormal and indicative of hepatic dysfunction This form of the test is unreliable because variations of intestinal absorption and renal excretion change the results independently of hepatic function The abnormal galactose tolerance test in hyperthyroidism depends at least in some measure on the increased rate of intestinal absorption

Intravenous test The intravenous galactose tolerance test eliminates these defects and is

extolled by Althausen as a most reliable test of hepatic function

Procedure After a blood sample is obtained for analysis the patient is given

1. 1 cc of a 50% solution (0 5 gm) of galactose per kilogram of body weight intravenously This is injected with a 100 cc syringe over a period of 4 to 5 minutes
2. 75 minutes later another specimen of blood is withdrawn
3. Glucose is removed from both samples of blood by fermentation with yeast
4. Both filtrates are analyzed for reducing substance
5. The nongalactose reducing substance in the fasting sample of blood is subtracted from the total reducing substance in the second specimen to obtain the galactose value

Interpretation Normally less than 20 mg % of galactose is present at the end of 75 minutes Althausen (1948) and Bassett and associates (1941) found this test almost invariably negative in extrahepatic obstruction and very frequently abnormal (positive) in parenchymatous jaundice It is undoubtedly a useful test in determination of hepatic damage and especially in the differential diagnosis of jaundice (see Chapter 14) However because of its drawbacks other tests largely replace it in most laboratories The galactose is expensive and most clinical laboratories are not set up for the fermentation procedures

Galactose clearance time Barnes and King suggested a formula for calculating the disappearance of galactose from the blood Its technique is similar to that in the intravenous test described above but a formula is used to calculate the *galactose time* *The mean of* this value in 41 normal subjects was 61 minutes with a range of 30 to 9 minutes Like the other galactose tests it was proposed for u e in thyrotoxicosis

5 *Le ulose Tolerance Test*

The levulose tolerance te t is based on principles similar to the galactose tolerance test The administration of 50 gm of levulose to a normal individual results in little or no rise of the blood sugar at the end of one or two hours A 15 mg rise of the blood sugar at the end of two hours is considered the upper limits of normal This test is more of historical and theoretical than practical interest It is neither as sensitive nor as easy to perform as some of the other carbohydrate tests

6 *Lactate Clearance Test*

The function of the liver to convert d lactate into glycogen has been utilized as a test of hepatic function Injection of 75 mg of sodium d lactate per kilogram of body weight into a normal person results in disappearance of the injected lactate within 30 minutes The test utilizes this procedure and the retention of over 5 mg % at the end of 30 minutes is considered a sign of abnormal hepatic function

7 *Pyru ic Acid Elevation*

Pyruvic acid is one of the intermediary products of carbohydrate metabolism Even more important it forms a focal point where the other foodstuffs proteins and fats meet and may be reconverted into each other Thus pyruvic acid can be converted into lactic acid and eventually oxidized into CO and H_2O or it may be aminized to form the amino acid alanine or proceed to form fatty acids (oxalacetic malic fumaric acid etc) Conversely amino acids and fatty acids may be metabolized by way of pyruvic acid

Normally however pyruvic acid is present in the blood in minute amount

It was observed by Snell and Butt in 1942 that in hepatic coma there is a rise in blood pyruvic acid More recently Amatuzio and Nesbitt found this sub tance in increased amounts in the blood and spinal fluid of patients with liver disease The elevation was more marked in those with hepatic coma These patients did not suffer from thiamine deficiency which is one of the causes of increased blood pyruvic acid It is another example of the profound metabolic disturbance in liver disea e

6 — Protein Metabolism

THE liver plays a primary role in the important field of protein metabolism The ingested proteins are broken down into amino acid in the gastrointestinal tract and from there absorbed and transported via the portal vein to the liver Less than 20% of the amino acids pass the liver unmodified

Eighty per cent of the amino acids undergo changes in the liver along one of the following three pathways (1) deaminization (2) transamination and (3) protein synthesis

Deaminization with urea formation is accomplished chiefly in the liver and to a lesser extent in the kidney and other tissues After hepatectomy urea concentration of blood and tissues and urine falls (Bollman and co workers 1924) while the concentration of amino acids rises (Freeman and Svec 1951) The urea is excreted and the fatty acid residue is either oxidized or converted to fat or to glucose and finally to glycogen Some of the amino acids are transformed into other amino acids and resynthesized into proteins

Protein synthesis is one of the most important functions of the liver The maintenance of the serum proteins is largely dependent on the liver It must not be overlooked however that the intestine is an important site of protein synthesis (Tarver and Schmidt 1942, Friedberg 1947) Albumin is chiefly synthesized in the liver The origin of the various globulins has not been clearly elucidated but some of them are probably synthesized and destroyed in the liver The ability of the liver to synthesize protein is demonstrated dramatically by rapid synthesis of plasma proteins after plasmapheresis and the rapid regeneration of the liver after partial hepatectomy Injury of the hepatic cells retards or arrests this process The raw materials amino acids or other proteins must be made available for the synthesis This task is accomplished with the help of a group of enzymes known as proteinases The liver, likewise synthesizes fibrinogen In hepatectomy, or severe liver necrosis this protein fraction is markedly reduced however in mild hepatic damage, the fibrinogen may even be increased

Among special proteins prothrombin is an outstanding product of the liver Prothrombin a protein carbohydrate combination is chiefly formed in the liver After hepatectomy, the prothrombin co prothrombin and fibrinogen are decreased rapidly (Mann and co workers 1951) Vitamin K is necessary for its formation when this vitamin is not available to the liver hypoprothrombinemia results This vitamin is found in abundance in foods and because of its intestinal synthesis by bacteria, it is virtually impossible to produce avitaminosis K in any mammals including man Sterilization of the intestinal tract with antibiotics may arrest the intestinal synthesis of this vitamin Bile is necessary for its absorption therefore in the absence of bile in the intestinal tract avitaminosis K and hypoprothrombinemia result from malabsorption Either an absence of vitamin K or the inability of the liver to utilize it results in the bleeding tendency due to hypoprothrombinemia

Originally vitamin K was isolated from alfalfa and called K_1 and from putrefying fish meal called K_2 K_1 is 2 methyl 3 phytyl 1, 4 naphthoquinone while K is 2 methyl 3 1 4 naphthoquinone Menadione is a synthetic compound referred to as vitamin K_3 and is 2 methyl 1 4 naphthoquinone The latter is widely used clinically and possesses marked prothrombinogenic activity Recently, Quick demonstrated in the dog that vitamin K_1 is much more effective in restoring the depleted prothrombin in the dog than menadione (K_3)

Whereas 9γ of K1 per kilogram restored the prothrombin to normal in four hours enormous doses of menadione restored the prothrombin to only 40% of normal He suggests that the synthesis of prothrombin depends upon a reaction between an apo enzyme and vitamin K or menadione

AE + K = AEK—prothrombin (100%)
AE + M = AEM—prothrombin (40% of normal)

The varied activities of the liver are demonstrated by the fact that while it produces prothrombin to aid coagulation it also produces heparin an anticoagulant The liver is the principal source of heparin and it is probably produced in the Kupffer cells

Antithrombin is another protein which has an anticoagulation function in the blood clotting mechanism The evidence that it is formed in the liver comes from animal experiments and clinical studies (Innerfield and collaborators) Animals poisoned with carbon tetrachloride and patients with progressive liver failure show decreased blood antithrombin levels Elevated antithrombin levels occur in acute pancreatitis pancreatic cysts and carcinoma of the pancreas It is likely that the liver produces the inactive form or antithrombinogen which is activated by trypsin of pancreatic origin

Tests Utilizing Protein Function of the Liver

Serum Proteins

The depression of blood proteins in patients with liver disease was observed over two decades ago (Wiener and Wiener 1930) In 1935 Foley Keeton and Kendrick reported depression of serum proteins in patients suffering from severe liver disease and a drop of plasma protein was observed by them in dogs receiving acacia injections

Originally an alteration in circulating proteins was considered a sign of advanced hepatic disease and therefore of no value as an index of early hepatic dysfunction This erroneous concept was formulated on the observations made with the crude Howe technique for analyzing serum and plasma proteins With this salting out technique a portion of the globulins is included in the albumin fraction and hence gives an erroneously high value for albumin

Serum Glycoprotein (Mucoproteins)

The glycoproteins or mucoproteins are carbohydrate protein complexes The carbohydrate is a polysaccharide and the protein to which it is bound has an electrophoretic mobility of gamma globulin Increased serum content of these substances has been noted in a variety of diseases metastatic neoplasm pulmonary tuberculosis other inflammatory conditions and myocardial infarction Recently a disturbance of the mucoprotein content of serum was noted in uncomplicated hepatitis and cirrhosis This abnormality consisted of a decrease of the protein fraction (M) and the maintenance of the polysaccharide fraction (P) at a normal level Thus the P M ratio was increased in liver disease and this ratio decreased to a normal range during recovery Similar alterations were noted in multiple myeloma This decrease of mucoprotein (M) and the increase of P M ratio is attributed to liver dysfunction (Greenspan and co workers 1951)

Electrophoretic Protein Fractionation

The introduction of the electrophoretic procedure by Tiselius in 1937 for the fractionation of plasma proteins revolutionized our concept of this problem With this method it is possible to estimate accurately the albumin as well as the various globulin fractions and fibrinogen The globulins are separated into the $alpha_1$ $alpha_2$ beta and gamma globulins The relative proportion of these fractions show an alteration *early* in parenchymatous liver disease The subfraction $gamma_1$ globulin is increased especially in cirrhosis (Franklin et al)

The normal values for the plasma proteins by the electrophoretic procedure are given by Kekwick and Nicholas as albumin 55% alpha globulin 14% beta globulin 13 5% gamma globulin 11% and fibrinogen 6 5% Leutscher gives the average values as follows albumin 6 3 gm alpha globulin 0 7 gm beta globulin 1 3 gm and gamma globulin

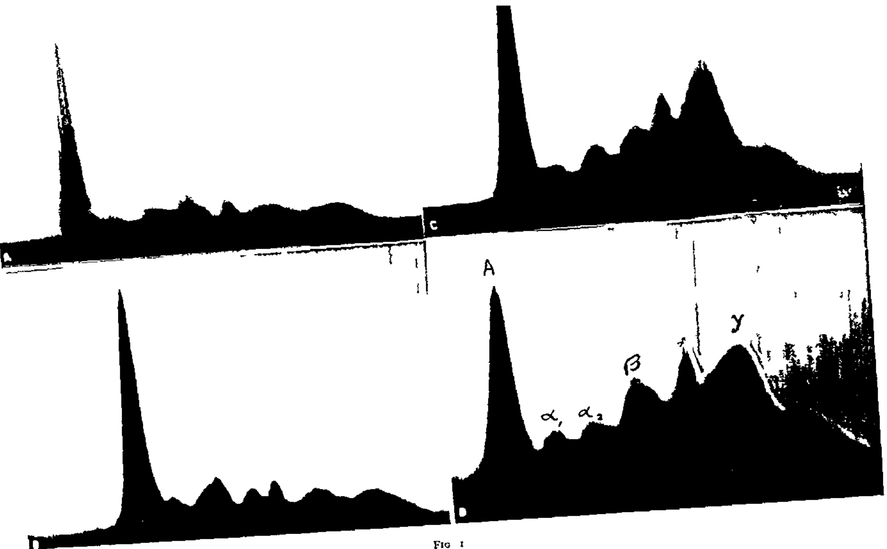


Fig 1

1.3 gm. Martin reports the following normal variations: albumin 5.8 to 6.[illegible] gm., alpha globulin 0.95 to 1.4 gm., beta globulin 1.1 to 1.4 gm., and gamma globulin 1.0 to 1.4 gm. These values in grams are slightly high. The average normal values given by Rickets and his group are more in accordance with my experience: albumin 3.93 gm. to 4.70 gm., and average globulin values as follows: alpha 0.96 gm., beta 0.89 gm., and gamma 0.9[illegible] gm. The variations depend to some extent on the buffer used and the pH of the electrophoretic medium.

Electrophoretic studies done on patients with parenchymatous liver disease, both cirrhosis and hepatitis, show decrease in albumin and elevation of the gamma globulin. The elevation of the latter is evident even in mild liver disease when the total protein remains normal. The decrease in the albumin is very slight and may not be obvious in mild parenchymatous hepatic disease but becomes more marked in severe liver disease. Elevation of the beta globulin occurs in certain types of liver disease, such as biliary cirrhosis, in which there is a concomitant rise in plasma lipids. This rise in the beta globulins may depend upon the elevated plasma lipids and the inherent fallacy of the technique. The lipids are carried by the alpha and beta globulins and travel in the same electrophoretic sphere with these globulins. Therefore, the deflection in the electrophoretic diagram may be due to the lipids rather than the protein. Occasional elevations in the alpha globulins are also seen in infectious hepatitis.

While the electrophoretic determination of plasma protein is a valuable test for detecting hepatic injury, it requires expensive apparatus and is too time consuming for the clinical laboratory.

Chemical Protein Fractionation

Wolfson and co-workers (1948) described a chemical procedure for separating the albumin and globulin fraction; the results closely approximate the values obtained by electrophoresis. We (Spellberg and co-workers, 1950) used this technique in studying patients with hepatitis and various types of cirrhosis and found the gamma globulin elevation a reliable and early sign of hepatic dysfunction. It was more accurate in this respect than the cephalin-cholesterol flocculation test, the thymol turbidity and flocculation test, the bromsulphalein test and the cholesterol ester ratio (see Table 7). It was abnormal in patients with very early cirrhosis and remained elevated for a long period in patients convalescing from hepatitis.

In the severe types of cirrhosis, especially those with ascites, the albumin was markedly depressed while the gamma globulin was markedly elevated. The ratio of the gamma globulin to the albumin (γ/A) was even more conspicuously disturbed than either of these absolute values (see Figure 75). This disturbance of the γ/A ratio is therefore a valuable prognostic test. This chemical procedure for fractionating the serum proteins is a valuable clinical test in the study of hepatic disease and should be utilized more widely.

Fig. 1. Electrophoretic diagrams (Published through the courtesy of Dr. Smith Freeman, Research Service, Hines Veterans Administration Hospital, Hines, Illinois.)

A. Normal

B. Patient with ulcerative colitis

Albumin	47.[illegible]0%
Alpha 1 Globulin	6.68%
Alpha 2 Globulin	15.[illegible]0%
Beta Globulin	7.95%
Fibrinogen	8.8[illegible]%
Gamma Globulin	1[illegible].5[illegible]%

C. Patient with portal cirrhosis

Albumin	1[illegible].8[illegible]%
Alpha 1 Globulin	5.44%
Alpha 2 Globulin	8.10%
Beta Globulin	10.6[illegible]%
Fibrinogen	13.55%
Gamma Globulin	1[illegible].[illegible]1%

D. Patient with biliary cirrhosis

Albumin	4[illegible].15%
Alpha 1 Globulin	5.5[illegible]%
Alpha 2 Globulin	8.50%
Beta Globulin	1[illegible].[illegible]%
Fibrinogen	14.97%
Gamma Globulin	9.78%

TABLE 7

Abnormal Globulin Concentration Compared with Other Tests of Liver Function

D g o	N Pt	Glob Abn	C C F	T T	T F	B S P	Alk P n Pho ph ta
Portal Cirrhosis Severe	4	9/9	6/8	2/8	1/8	1/1	3/6
Portal Cirrhosis Mild	4	9/11	2/12	1/12	0/12	7/9	0/7
Xanthom Bil Cirrhosis	2	14/14	4/12	13/13	6/13		12/12
Banti s Syndrome	3	5/7	3/7	2/7	0/7	1/7	0/5
Acute Hepatitis	12	26/50	15/47	18/43	3/45	3/15	5/37
Infectious Mononucleosis	3	2/10	6/10	4/10	3/10	1/7	2/7
Total	28	65/101	36/96	40/93	13/95	13/39	22/74

M A Spellberg et al Gastroenterology 41 1 1950

Numerator represents number of positive tests Denominator represents total number of tests

A report from Holland by Verschure and Janssen confirms the excellent correlation of the albumin and globulin deviations with the functional capacity of the liver They used a different method of determining the proteins

Gamma Globulin Turbidity Test

Averga and Popper (1950) suggested a turbidimetric modification of Wolfson and Cohn s test for gamma globulin The degree of turbidity is proportional to the gamma globulin content and can be expressed in grams per 100 cc or as units These workers corroborated the close correlation between this chemical estimation and the electrophoretic determination However Rickets and co workers found a good deal of discrepancy between the turbidimetric (ZnSO$_4$ (NH$_4$)$_2$ SO$_4$ NaCl) methods of globulin estimation and the electrophoretic procedure The reason for this discrepancy is not apparent While this limited turbidimetric procedure may be worth while under certain circumstances it seems that if the Wolfson and Cohn method is utilized it should be carried out in toto and the albumin determination carried out as well For as was pointed out before the ratio between the gamma globulin and the true albumin is of clinical value

Zinc Sulfate Turbidity Test

Kunkel suggested a turbidimetric test by which serum is treated with a reagent containing zinc sulfate barbital and sodium barbital The turbidity which is read in a spectrophotometer is proportional to the globulin concentration The correlation of this turbidity test with the gamma globulin is not as good : the tests described above The prec formed is influenced by the serum albun lipids as well as the gamma globulin T is inhibited by bile as well as lecithin] theless Kunkel and co workers foun turbidity test abnormally elevated in p with hepatitis and various types of cir The normal range is 4 to 12 units w *average of 8 units The highest valu* found by them in post hepatitic cirrhosis

Photometric Determination of Gamma Gl

More recently (195-) Saifer and co w described a flocculation procedure for g globulin using the cephalin cholesterol sion in the presence of Hayem s solutio *testing the precipitate for proteins by the* tometric ninhydrin procedure When th tings of the test such as pH temper time and concentration of reagents are fully controlled the determination of pu gamma globulin coincides well with r obtained with the electrophoretic me However the presence of fibrinogen and globulin fractions yielded erroneously results They therefore applied the proce in a modified form to human sera by cipitating the gamma globulin by mear 20% sodium sulfite and applying the floc tion reaction to the dialyzed globulin The results thus obtained were comparab those obtained with the electrophoretic cedure

This procedure is undoubtedly less labo than the electrophoretic procedure, but

more complicated than the others described Its greater accuracy awaits confirmation

Among the other tests that depend upon disturbance of the serum proteins are

1 cephalin cholesterol flocculation test
2 thymol turbidity test
3 colloidal gold test
4 colloidal red test

Cephalin Cholesterol Flocculation Test

The cephalin cholesterol flocculation test was introduced by Hanger in 1939 The mechanism of the test was later elucidated by Moore and co workers with the use of purified plasma proteins They demonstrated that an elevation of the gamma globulin concentration induces flocculation whether the gamma globulin is from normal individuals or patients with hepatitis Normal albumin inhibited this reaction while albumin derived from patients with hepatitis had no effect Therefore a positive test indicates an increase of gamma globulin and a decrease in quantity as well as alteration in quality of the serum albumin

The degree of flocculation is measured as 1 to 4 plus and the flocculation is read in 48 hours Normal sera should show no flocculation in 48 hours Because of the inherent errors of the test 1 + flocculation may be sometimes seen in normal persons and therefore should not be regarded as positive evidence of hepatic dysfunction

It has been demonstrated by various observers that this test procedure must be carefully standardized to avoid many false positive reactions The following factors affect results of the cephalin cholesterol flocculation test

1 Overripening of the cephalin by exposure to light
Increasing the temperature of the room where flocculation reaction is done (37 5° C or above)
3 Exposure of the reaction or serum to ultraviolet light and
4 Dilution of the serum

All tend to produce false positive reactions

These shortcomings of the test have been overcome by use of a standard commercial cephalin and by standardizing the laboratory environment of the test

Modifications of cephalin cholesterol test Various proposals have been made to increase the sensitivity or accuracy of the test Among these are suggested changes in the preparation of the cephalin cholesterol emulsion and serial dilution of the serum (Frisch and Quilligan) and quantitation of the procedure expressed in cholesterol units (Saifer) The cholesterol units are directly proportional to the amount of cholesterol in the flocculate which is always below 100 units in the normal but is markedly increased in abnormal sera While these modifications are of interest from the investigation point of view they are too cumbersome for the average clinical laboratory Moreover they may not yield sufficient added information of importance to the clinician than the well standardized Hanger method of performing this test

Thymol Turbidity Test

MacLagan in 1944 introduced the thymol turbidity test as an indicator of hepatic dysfunction The addition of an aqueous mixture of thymol and barbital to sera of patients with liver disease resulted in turbidity while normal sera showed no such reaction The degree of turbidity is expressed in units 0 to 5 units may be considered normal although the upper limit of normal varies from 3 to 5 in different laboratories The precipitate is a protein thymol phospholipid complex The quantitative composition is as follows protein 37 5% thymol 32% cholesterol 16 5% and lecithin 8 0% One unit of turbidity is equal approximately to 106 mg of precipitate per 100 cc of serum this is equivalent to 40 mg of protein

The thymol turbidity like the cephalin cholesterol flocculation is activated by gamma globulin and inactivated by albumin The protein of the precipitate is chiefly gamma globulin however increased serum lipids are known to increase the thymol turbidity test and even to produce false positive reactions Since the serum lipids are transported by and loosely attached to the beta and to a lesser extent the alpha globulin these protein fractions have an indirect influence on this test

This relationship of the thymol turbidity test to the gamma globulin elevation is not a

direct or quantitative one In hepatitis cholangiolitic cirrhosis and other inflammatory diseases of the liver there is a good correlation between the hypergammaglobulinemia and the thymol turbidity test However in nutritional cirrhosis and fatty livers the thymol turbidity test may be normal or nearly normal in spite of considerable elevation in the gamma globulin The marked hypergammaglobulinemia of multiple myeloma may be accompanied by a normal or slightly elevated thymol turbidity This suggests that a qualitative modification of the gamma globulin as well as a quantitative increase of this fraction is involved in the production of a positive test

Thymol Flocculation

MacLagan noted that while normal gamma globulin was capable of producing turbidity only the gamma globulin from patients with hepatitis produced flocculation This also suggests a qualitative change in the gamma globulin The rationale of the thymol flocculation test the most commonly used modification of the original test is based on the occasional divergent responses of the two tests in the same subject The thymol turbidity test is read within 30 minutes but the thymol flocculation in the same mixture is determined within 18 hours and like the cephalin cholesterol flocculation reported as 0 to 4 plus a flocculation of 1+ is accepted as normal It is simple to perform these two tests together since additional information may be obtained both can be done without much additional effort The thymol flocculation test may be positive in certain types of hepatic disease while the thymol turbidity is negative This may be noted especially in cases of chronic smoldering hepatitis

Modifications of the Thymol Precipitation Tests Shank and Hoagland suggested a modification of the thymol turbidity test by quantitative determination of turbidity in a spectrophotometer and comparison with a barium sulfate standard Ley and co workers used the Evelyn photoelectric colorimeter to quantitate the degree of flocculation Shay and co workers proposed the 18 hour turbidity ratio This refers to the ratio of the turbidity at 30 minutes as compared with the supernatant turbidity at the end of 18 hours or the period allowed for flocculation—the 18 hour value being the numerator and the 30 minute value being the denominator of this fraction As flocculation occurs the turbidity at 18 hours decreases therefore the higher the flocculation the lower is this ratio The normal value for this ratio is 85% or above Patients with hepatic disease very frequently show abnormally low ratios

Colloidal Gold Test

The colloidal gold test (Gray 1940) of the serum is performed similarly to the colloidal gold test of the spinal fluid The normal and abnormal values were originally expressed in the form of a curve as in the Lange test This has been modified (MacLagan 1944) and is expressed as 0 to 4+ or 5+ Readings above 1+ are regarded as abnormal This test like the ones described above also depends on an elevation of the gamma globulin and depression of serum albumin but does not parallel the other tests in all situations Armas Cruz and coworkers (1952) recently confirmed the observations of other workers about the accelerating effect of gamma globulin and retarding effect of albumin on the cephalin cholesterol flocculation colloidal gold and colloidal red test The thymol turbidity test required globulin from pathologic sera The mechanisms involved in the flocculation reactions were reviewed by these workers

Colloidal Red Test

The colloidal red test another flocculation test consists of the determination of the degree of flocculation of colloidal solution of scarlet (sudan IV) red by serum over a period of 24 hours (Ducci 1947) The test is not affected by refrigeration preservation or exposure of serum to light The flocculation is expressed as 0 to 4 or 5+ Values of 2+ or more are considered abnormal It like the other flocculation tests depends upon an increase of serum globulin According to some observers (Strade and associates) it is likely to give fewer false positive results in patients without hepatic disease and is selectively positive in patients

with inflammatory liver disease and negative in degenerative liver disease Others (McIntire and associates) praised its sensitivity but made no distinction between various types of liver disease

Takata Ara Reaction and Other Flocculation Tests

This reaction depends on flocculation of a solution of mercuric chloride by elements of the serum tested It probably also depends upon a disturbed relationship of the serum albumin and globulin This test has been largely replaced by the newer flocculation tests The formol gel test and Weltmann s reaction are no longer used as indices of hepatic dysfunction

Steinberg proposed a modification of the cephalin cholesterol flocculation test by substituting desoxycholic acid for the cephalin in the reagent He claimed improved stability for the mixture and good correlation of this test with the conventional Hanger test The utilization of Hayem s solution* in a flocculation test was suggested by Mandel and Paris This flocculation reaction also depends on an elevation of the gamma globulin but is less specific than some of the other flocculation reactions

Amino Acid Tolerance Test

Since one of the functions of the liver is to break down amino acids or synthesize them into body proteins the use of an amino acid loading test was proposed Forty cubic centimeters of a 10% casein hydrolysate is injected intravenously and blood amino acid nitrogen is determined before and 5 15 35 and 95 minutes after injection Actually only the 35 and 95 minute determinations need to be done since one third of normal subjects show a fasting level at 35 minutes and the rest show a fasting level at 95 minutes (Lyttle and co workers 1943) The average fasting alpha amino acid nitrogen is 4 5 mg % Patients with hepatic damage show a slow return of the fasting level however the rapidity of renal excretion may influence and invalidate these results There fore for accuracy of interpretation quantitation of urinary amino acids should be done simultaneously

Tyrosinemia and Tyrosinuria

In diffuse liver disease tyorsine is one of the amino acids that appears in the blood stream and urine Fasting normal subjects show no tyrosine in the blood filtrates or urine For this reason tyrosinuria or tyrosinemia is a sign of the inability of the liver to utilize this amino acid and therefore a sign of hepatic injury (Jankelson) Blood protein tyrosine level was found elevated in many patients with infectious hepatitis (Wartman and Shlimovitz 1946) However tyrosine is not universally detected in the blood in even fatal cases of liver disease Its presence is therefore good evidence of diffuse liver injury while its absence does not exclude it

Cystinuria

Dent and Walshe have observed a rise in urine cystine levels in patients with various hepatic diseases and have suggested this as a sensitive indicator of hepatic damage

Blood Urea Nitrogen

From theoretical considerations one should expect a marked drop in urea nitrogen in severe diffuse hepatic disease This is actually very rare occurring only in an occasional case of rapidly progressing hepatic necrosis In contrast the frequent association of renal damage with severe hepatic disease (hepatorenal syndrome) results in an elevation of the nonprotein nitrogen By using urea and creatinine clearance tests Meyer and co-workers came to the conclusion that urea nitrogen elevation in liver disease is due to increased tubular absorption of urea (Chapter 65 p 479)

Prothrombin Time

A reduction of the amount of prothrombin or an increase of prothrombin time may be due to inability of the liver to synthesize the prothrombin or may be due to lack of absorption of vitamin K in the absence of bile in the intestine Hypoprothrombinemia in a mildly icteric patient who shows bile pigment in the

*Hayem solution = mercuric bichloride 0 5 gm sodium sulfate 5 0 gm sodium chloride 1 0 gm distilled water 1000 cc

feces must be due to failure of synthesis in the liver (providing no dicumarol or antibiotics have been administered) Hypoprothrombinemia in my experience is a late manifestation of severe hepatic damage and is more valuable as a prognostic rather than a diagnostic test Mann Butt and Hurn advise the use of the two stage method of prothrombin determination as a more sensitive index of hepatic dysfunction than the one stage procedure

Vitamin K Response Test

The frequency of jaundice in severe liver disease requires that in a patient with hypoprothrombinemia the nonabsorption of vitamin K must be ruled out before the hypoprothrombinemia can be attributed exclusively to hepatic factors To solve such a dilemma the vitamin K tolerance or response test was introduced The parenteral administration of vitamin K results in a rapid fall of the prothrombin time (rise in prothrombin) if biliary obstruction is the cause of the deficiency The prothrombin time fails to respond to vitamin K if liver injury is responsible for the hypoprothrombinemia Lord and Andrus advised a 2 mg test dose intramuscularly and Seligman and co workers used a 10 to 20 mg dose intravenously I believe the larger dose should be used either intravenously or intramuscularly The vitamin K response test is an excellent aid in differentiating jaundice of hepatic and extrahepatic origin but not as a liver function test since most patients with mild liver disease show no hypoprothrombinemia

Vitamin K Tolerance Test

Unger and Shapiro proposed what may be termed a true vitamin K tolerance test which can be utilized in individuals showing abnormal prothrombin time This test depends upon the administration of large doses of vitamin K intravenously with a resultant paradoxical increase in prothrombin time The further deterioration of prothrombin production is postulated as being due to a more rapid exhaustion of the substrate required for prothrombin synthesis or an abnormal use of this substrate

Technique The test is done as follows 76 mg of synthetic vitamin K* is injected intravenously on four successive days

1 Prothrombin level is determined by using diluted (12.5%) plasma for several days prior to the vitamin K administration
2 Prothrombin determination is done daily during the administration of the vitamin K
3 Interpretation A negative or normal response is one in which there is
   a no significant rise in prothrombin time from the resting level
   b a return of an abnormally high prothrombin time to a normal level or
   c reduction of a normal prothrombin time to lower than normal level
4 A positive or abnormal test is one in which there is
   a failure of an abnormally high prothrombin time to return to normal
   b a further elevation of an abnormal prothrombin time or
   c a transient rise of a previously normal prothrombin time to more than 47 seconds

While Unger and Shapiro claim that this test is quite sensitive and comparable to other liver function tests it is not practical since it requires five days or more for its completion and entails a good deal of laboratory work Moreover since it results in interference with one of the vital functions of the liver it may not be entirely innocuous

Dicumarol (Dicoumarin) Response Test

It is likely that patients with hepatic dysfunction may show an abnormally severe response to dicumarol administration Reisner and co workers found that patients with hepatic disease showed a depression of prothrombin activity to 60% or less of normal value from administration of 100 mg of dicumarol and suggested this as a test of liver function

* Synkavite tetrasodium 2 methyl 1 4 naphthohydroquinone diphosphoric acid ester

Plasma Antithrombin Titer

A decrease of plasma antithrombin titer has been noted in severe diffuse hepatic necrosis and extensive metastatic neoplasms of the liver (Innerfield and co workers 1952). Antithrombin was normal in mild and moderately severe liver disease in spite of marked abnormality of other liver function tests; however, it was abnormal and showed progressive fall in active progressive hepatic decompensation and necrosis. This test is therefore not useful in detecting liver damage but may be utilized as a prognostic test in determining progressive hepatic cell necrosis. There was a parallelism between a rise and fall of this titer and the regression or progression of parenchymal necrosis and failure. It is curious that antithrombin and prothrombin substances with opposing activities in the clotting mechanism are both decreased in severe liver failure.

7 — Fat Metabolism

Neutral Fats and Fatty Acids

THE role of the liver in fat metabolism is no less important than that in carbohydrate or protein metabolism. It is estimated that 60 to 70% of ingested fat is transported by the lymphatics after absorption, while about 30 to 40% is transported by the capillaries to the portal circulation and thus passes through the liver. Some fat is stored in the liver normally (5 to 6%) and under the impact of dietary aberration and noxious agents this may increase tremendously (to 50 to 60%) (Chapter 42).

The liver has the capacity of modifying fatty acids by changing the length of the carbon chain and by changing their degree of saturation. The liver contains a greater proportion of unsaturated fatty acids, and slices of liver tissue have been observed to form unsaturated fatty acids in vitro. The liver can also form fats from carbohydrates and amino acids with the aid of thiamine chloride and other members of the B complex. It is the principal site of origin of ketone bodies.

Phospholipids

Phospholipids are not formed exclusively by the liver but are synthesized there at a higher rate than in any other organ except in the intestine during absorption. The intestinal formation of phospholipids is apparently chiefly a mechanism for absorption. The plasma phospholipids originate chiefly in the liver. This has been shown by the P^{32} studies of Chaikoff's group (Fishler and associates). The role of lipotropic agents in phospholipid synthesis in the liver is discussed in Chapter 40.

Cholesterol

The role of the liver in cholesterol metabolism is important not only from the point of view of hepatic physiology and pathology but because it may hold the key to the riddle of atherosclerosis. The cholesterol in the mammalian organism comes from exogenous and endogenous sources. Absorption of cholesterol from ingested food accounts for only a portion of this steroid. While other tissues (especially intestine) are capable of synthesizing cholesterol, the liver seems to be the organ chiefly

Table 8

Plasma Cholesterol after Ligation of Common Bile Duct Cholesterol

H	T t l	F	F t
0	59	1	46
6	86	4	44
1	111	57	54
4	1 4	8	43
48	75	5	50

From Byers Friedman and Michaelis J Biol Chem *188* 637 1951

responsible for maintaining the normal plasma cholesterol This has been demonstrated by radioactive tracer studies (Gould) as well as in studies in hepatectomized animals which have difficulty in restoring a depleted plasma cholesterol (Friedman and co workers 1951) Even endogenous cholesterol may pass through the liver where it is converted into lipoproteins (Gould)

The liver excretes cholesterol in the bile for this reason the rise in total cholesterol in common duct obstruction was glibly attributed to impairment of excretion Byers and co workers recently stated that this assumption is probably erroneous Ligation of the common bile duct results in a rise in serum total cholesterol which is prevented by partial or total hepatectomy Parenteral administration of cholesterol did not affect the rate of cholesterol increase These observations suggest that liver synthesis is an important factor in the rise of plasma cholesterol after biliary duct obstruction Failure of excretion of free cholesterol is probably of secondary importance

Some evidence presented recently by Bailey and Freeman suggests that hepatic damage may interfere with cholesterol catabolism as well

Table 9

Results of Total Lipid Determinations with the Phenol Reagent in Patients with Various Types of Liver Disease

	D gno	N of C	T b d ty L t R g	A e g
1	Normals	6	16–30	21
	Post h patitis cirrhosis	7	6– 8	14
3	Alcoholic cirrhosis	6	7–34	16
4	Unclassified cirrhosis		3 50	2
5	Cholangiolitic cirrho s	10	36–1 5	78
6	Fatty liver	6	38–60	47

Eck fistula dogs fed cholesterol showed a greater rise in the blood and liver cholesterol than the normal controls This rise in the liver cholesterol indicates that the blood rise is not due to simple shunting of the absorbed cholesterol away from the liver

Esterification of cholesterol is a function of the liver that is even more readily disturbed by disease of this organ After partial hepatectomy and induced hypocholesteremia the free cholesterol is more quickly restored than the esterified cholesterol Hepatic injury results in a decrease of cholesterol esters long before the total cholesterol is depressed Duct ligation in animals does not result in a rise in the esterified cholesterol This fraction is maintained at the same preoperative level The rise is entirely in the free cholesterol fraction (Table 8)

Tests Dealing with Lipid Metabolism

Total Serum Lipids and Phospholipids

The total serum lipids as well as the phospholipids increase in biliary obstruction In mild hepatocellular damage the lipids may be normal or slightly depressed however in severe and increasing hepatic damage the total as well as the phospholipid values fall Hence this determination may be of some prognostic value Biliary cirrhosis, such as the cholangiolitic and xanthomatous types differs in this respect from portal cirrhosis by the presence of hyperlipemia In xanthomatous cirrhosis the serum looks grossly clear and not lipemic because of the predominant increase in phospholipids rather than neutral fats Patients with fatty livers may also show increased serum lipids before the development of cirrhosis hence this test may be useful in differentiating the two conditions

Kunkel and co workers (1948) introduced a turbidimetric test to estimate the total serum lipids it has an advantage over the quantitative chemical methods because of its simplicity The reagent consists of 1% liquid phenol and 12% NaCl in distilled water The normal values are 16 to 30 turbidity units with an average of 21 They found their cirrhotics to have normal or low lipid turbidity but patients with cholangiolitic cirrhosis and fatty livers showed high values (see Table 9)

Fat tolerance test

This test which is not of practical importance attempts to utilize the homeostatic effect of the liver on blood lipids The test is carried out (Sullivan and Fershtand 1935) as follows

1 Fasting serum lipids are determined
2 100 gm of cottonseed oil is administered orally after a 15 hour fast
3 Serum lipids are determined 3 6 and 9 hours after administration of the test dose

Interpretation In the normal person in the studies reported the lipids rose 65% above the fasting level at six hours but returned to normal at nine hours In patients with liver disease the rise was not as high as in the normal and the lipids did not fall to the fasting level at nine hours These results would indicate defective absorption as well as defective catabolism

Serum Cholesterol and Cholesterol Esters

In normal subjects the total serum cholesterol may show considerable variation (120 to 300 mg %) but the percentage of esterified cholesterol is maintained at a level of 65% or more of the total cholesterol value The esterification of cholesterol is disturbed early in liver disease and a depression of the serum cholesterol esters is a sensitive indicator of hepatic disease The cholesterol esters may decrease to very low levels (10%) or disappear from the blood completely Such marked depression of cholesterol esters usually occurs in severe hepatocellular disease however in itself it is not of great prognostic significance I have seen cholesterol ester values around 10% in patients with hepatitis who did not appear very ill clinically and who made uneventful recoveries This is especially true when the total cholesterol is normal or only slightly depressed (Table 51)

The total cholesterol is not as important as the esterified cholesterol in the diagnosis of hepatocellular injury however the total cholesterol does show variations in clinical hepatobiliary disease In diseases accompanied by obstruction to the bile flow the total cholesterol usually rises In severe hepatocellular damage the total cholesterol as well as the esterified fraction falls this total depression of cholesterol metabolism is a grave prognostic sign In mild or moderate parenchymal damage the total cholesterol remains normal this determination by itself is therefore of no value in the diagnosis of minimal hepatic injury

The absolute value of the esterified cholesterol is of clinical significance especially when the total cholesterol is increased as is the case in hepatic obstruction For when the total cholesterol is considerably increased the percentage of esterified cholesterol may be low and yet the absolute value may be perfectly normal A low absolute cholesterol ester value may signify a poor surgical risk Greene regards a patient with obstructive jaundice and cholesterol ester concentration of less than 60 mg % as a poor candidate for surgery The use of cholesterol and cholesterol ester values in the differential diagnosis of jaundice is discussed in further detail in Chapter 14

8

Vitamins and Enzymes

Storage of Vitamins and Other Vitamin Functions

Vitamin A

The liver is important in the metabolism of vitamin A. It converts carotenes, or provitamin A, into vitamin A_1* and this vitamin is stored chiefly in the liver. The cirrhotic liver is poor in vitamin A, and defective storage may be one of the responsible factors. The vitamin A blood level does not show a normal rise after oral administration in patients with liver disease. In mild hepatic disease bile acids administered orally improve the intestinal absorption of vitamin A, while lecithin, which improves vitamin A absorption in sprue, has no such effect in hepatic disease (Adlersberg and associates 1948).

Thiamine

There is evidence of defective thiamine metabolism in liver disease. Thiamine chloride administered orally to normal subjects is rapidly absorbed and converted to diphosphothiamine. Patients with cirrhosis showed impaired formation of diphosphothiamine. Impaired phosphorylation of thiamine in advanced cirrhosis was also demonstrated by the slight rise in diphosphothiamine as compared to normal upon intravenous injection of cocarboxylase (Williams and Bissell).

Other Vitamins

The liver is likewise an important storage depot of various fractions of the vitamin B complex, vitamin C and vitamin D. The storage of vitamin D in the liver of cold blooded animals is a universally known fact, but the liver of mammals apparently stores this vitamin as well. The liver is important in the antirachitic activity of vitamin D as evidenced by the higher requirements of vitamin D to cure rickets in animals with hepatic injury (Heymann). However, cod liver oil, because of its unsaturated fatty acids, may have a deleterious effect on the liver.

Vitamin E, or alpha tocopherol, another fat soluble vitamin, has an important role in the nutritional production of hepatic necrosis (Chapter 40). Klatskin and Krehl noted some differences in the response of orally administered tocopherol in normal subjects and patients with cirrhosis. The significance of this is discussed in Chapter 43.

The liver is important as a storage place of the *anti anemic principle*. However, patients with cirrhosis have adequate stores of this principle. This function of the liver is therefore not easily impaired. The liver is also an important depot for iron storage (see Chapter 73). Blood iron values may become altered in liver disease, on which basis this determination has been suggested for the differential diagnosis of jaundice (page 94). *Serum iodine* is low or normal in cirrhosis and elevated early in hepatitis (Kydd and Man).

Serum Vitamin A and Vitamin A Tolerance Test

The plasma or serum vitamin A determination and the vitamin A tolerance tests may be helpful in the diagnosis and differential diagnosis of hepatic disease. The normal fasting vitamin A content of the serum is considered to be 60 micrograms per 100 cc, with a variation of 40 to 100 micrograms (Adlesberg and associates 1945). White and co-workers reported depression of the serum level of vitamin A in jaundiced patients with viral hepatitis and normal values in patients with common

* The conversion of carotenes into vitamin A also takes place in the intestine.

duct obstruction This can therefore be used in the differential diagnosis of jaundice

The administration of vitamin A orally to individuals with hepatic disease results in a slight or no rise of the plasma vitamin A value The oral dose used is 180 000 international units the blood vitamin A is determined four hours after the test dose and compared with the fasting level Normally the rise is in the neighborhood of 50% above the fasting level This lack of response to a large dose of the vitamin is probably an index of defective absorption rather than hepatic vitamin A depletion since no correlation between a flat vitamin A tolerance curve and hepatic stores of vitamin A has been found

Enzyme Regulation

The prolific chemical activities of the liver undoubtedly effect numerous enzymes and enzymatic reaction in the body The two enzymes on which liver physiology and pathology have a profound effect and on which there is a good deal of experimental and clinical data are alkaline phosphatase and cholinesterase

Alkaline phosphatase

The alkaline phosphatase activity is increased in skeletal disease in which there is increased osteoblastic activity For a while the osseous tissues were thought to be the only source of alkaline phosphatase Since this enzyme is normally excreted in the bile the rise of the serum alkaline phosphatase in obstruction of the common bile duct was thought to be due to failure of the liver to excrete the enzyme

Synthesis of Alkaline Phosphatase by the Liver

That the liver is not merely an excretory organ for alkaline phosphatase but actively elaborates the enzyme is suggested by the following observations

1 Serum alkaline phosphatase may be elevated in the absence of bile duct obstruction and skeletal disease
2 There is no direct correlation between bilirubinemia and hyperalkaline phosphatemia jaundice may be marked with only slight or no elevation of the alkaline phosphatase and this enzyme may be markedly elevated in mild icterus
3 Hepatectomy results in slight or no elevation of alkaline phosphatase while bile duct ligation results in marked elevation
4 Partial hepatectomy results in elevation of liver phosphatase followed by elevation of serum phosphatase
5 Ligation of one hepatic duct results in an elevation of alkaline phosphatase without hyperbilirubinemia and without decreased BSP excretion
6 Regenerating liver cells show increased concentration of alkaline phosphatase by histochemical techniques

It is therefore generally accepted that the liver is one of the extraskeletal sources of alkaline phosphatase Under the impact of certain noxious agents and pathological conditions the liver elaborates excessive amounts of this enzyme These conditions appear to be accompanied by active regeneration and the regenerating cells are the source of the increased phosphatase production

Excretion of Alkaline Phosphatase by Liver

Some confusion has arisen concerning the excretory functions of the liver as related to alkaline phosphatase There is no question that the liver excretes alkaline phosphatase into the bile but it is doubtful that the rate of excretion depends solely on the blood level of this enzyme The mechanism of excretion is probably more complex Two groups of observers (Cantarow and Miller 1948 Wang and Grossman 1949) have independently found that in normal dogs with duodenal fistulas transfusion of plasma with high alkaline phosphatase values obtained from dogs with common duct obstruction resulted in little increase of phosphatase excretion in the bile The plasma phosphatase remained elevated in these animals However Leveen and coworker found that alkaline phosphatase extracted from calves duodena and injected into dogs was rapidly removed from the plasma (in 1½ hours) and increased excretion in the bile persisted for 96 hours The question arises whether these two sources of alkaline phosphatase differ chemically or whether the blood in

TABLE 10

Method	Normal Value (Units)
Bodansky	–4
King Armstrong	3–13 (usually 5–10)
Huggins	3 15
Gomori Kaplan's Modification	0 8–4 5

TABLE 11

Alkaline Phosphatase Variations in Liver Disease

Disease Condition	
Common duct obstruction	E
Congenital atresia of bile duct	N
Biliary fistula	E
Infectious hepatitis	E or N
Laennec's cirrhosis	E or N
Biliary cirrhosis	E
Severe hepatic necrosis	N or L
High carbohydrate diet	E
Metastatic neoplasms of liver	E
Liver abscess	F

E = elevated N = normal L = low

regurgitation jaundice contains some substance that interferes with the excretion of alkaline phosphtase

Serum Alkaline Phosphatase as a Liver Function Test

The normal value of the serum alkaline phosphatase varies according to the method of determination therefore the units should be reported along with the method used The upper limit of normal values may vary from 4 Bodansky units to 15 Huggins units (Table 10)

Some have regarded a marked elevation of the alkaline phosphatase (above 10 Bodansky units) in a jaundiced patient as a sign of extrahepatic (post hepatic) obstruction this is not a safe assumption The majority of patients with common bile duct obstruction (post hepatic jaundice) have higher alkaline phosphatase values than patients with intrahepatic obstruction This however may not be true in individual cases Congenital biliary atresia is accompanied by normal alkaline phosphatase and is the only type of extrahepatic obstruction showing low values In the presence of normal flocculation tests normal protein values and normal cholesterol partition elevated serum phosphatase and bilirubin levels may be accepted as evidence of extrahepatic biliary obstruction The alkaline phosphatase may be markedly elevated in portal cirrhosis infectious hepatitis and metastatic carcinoma of liver *(even in the absence of jaundice)* It is frequently very high in various forms of biliary cirrhosis (cholangiolitic xanthomatous) One of our patients with biliary cirrhosis had a value of over 100 Huggins' units (Table 62)

The serum alkaline phosphatase is also of prognostic value Since normal and regenerating liver cells synthesize it in severe necrosis and lack of regeneration this enzyme rapidly decreases In this respect its level in the blood can be used as a criterion of hepatic function *A high and rising serum bilirubin level in the* presence of a low or falling alkaline phosphatase level is a grave prognostic sign Patients dying from liver failure show terminally low serum alkaline phosphatase (Table 11)

Cholinesterase

There is considerable evidence that the liver synthesizes cholinesterase and that the serum concentration of this enzyme is dependent upon hepatic activity Partial hepatectomy as well as hepatotoxic agents causes a fall of serum cholinesterase in animals The regeneration of this enzyme occurs at a much faster rate in normal persons than in patients with liver injury (Wescoe and associates) The decrease of serum cholinesterase in severe malnutrition is also attributed to the concomitant liver damage (Waterlow)

Serum Cholinesterase Test

The determination of serum cholinesterase as a test of liver function was first proposed by Antipol Tuchman and Antipol in 1938 Their method which consisted of measuring the liberated CO from a bicarbonate solution when acetyl choline was incubated with serum containing cholinesterase was cumbersome and did not come into general use Goldner and Morse used the Gomori method for estimating esterase in the serum They found this enzyme decreased in the serum in patients with liver disease and especially in cirrhosis Michel's procedure has been applied more widely clinically which has resulted in the stimulation of interest in this test This procedure consists of incubating serum with a barbital (Veronal)

phosphate buffer and acetylcholine. The liberation of acetic acid depresses the pH, which is measured by a pH meter. The cholinesterase *activity is expressed in terms of units of decrease* of pH per hour (ΔpH/hr.).* De la Huerga and coworkers (1952) utilized another method for determining the serum cholinesterase. *Their unit is equivalent to the micro*moles of acetylcholine bromide hydrolyzed per hr. per cc. of serum at 37° C. The normal values are 130 to 310 units.

Vorhaus, Scudamore and Kark found the normal range of serum cholinesterase activity to be between 0.68 and 1.37 units, with a mean of 0.94 units. In various forms of hepatocellular disease the range of activity was 0.09 to 0.86, with a mean of 0.46 units. In obstructive jaundice these values deviated insignificantly from the normal. These workers suggest this as a sensitive test for hepatic injury and valuable in differentiating hepatic from posthepatic jaundice. The usefulness of this test *has been confirmed by others* (Molander and associates, 1951). However, Mann and coworkers (1952) found cholinesterase determinations unreliable in differentiating hepatic from posthepatic jaundice; results were normal in chronic hepatitis. For this reason, they considered it of no help in following the course of hepatitis (Table 15).

Since synthesis of this enzyme parallels albumin (protein) synthesis in the liver, the *nature and origin of obscure hypoalbuminurias* may be clarified by this test. Thus, hypoalbuminemia due to defective hepatic synthesis *should be accompanied by low cholinesterase* values, while hypoalbuminemia due to other cause may show normal blood enzyme values.

* The figure obtained by the pH meter is corrected for nonenzymatic hydrolysis by using the table prepared by Michel.

9

Hormone Regulation, Water and Salt Metabolism

THE influence of the liver on hormone metabolism is most important since the ensuing alterations have a profound effect on the patient as a whole, not merely on specific biochemical processes of diagnostic importance. The ramifications of this function of the liver are discussed in greater detail in Section X. The liver inactivates estrogen and progesterone as well as testosterone. Estrogen inactivation by liver tissue has been observed in vitro as well as in vivo. The enzyme involved in this inactivation is apparently a protein. On reduced protein rations, this enzyme is synthesized with difficulty; *hence* estrogen inactivation is inhibited (Jailer and Seaman). *Vitamin deficiencies also impair* estrogen inactivation by the liver (Chapter 13).

Testosterone is also inactivated by the liver. In the rat, a niacin and tryptophan deficiency impairs inactivation of this hormone. In spite of the destruction of both testosterone and estrogen by the liver, in liver damage and especially *in cirrhosis, estrogen excretion in the* urine is elevated, while there is a depression in *17-ketosteroid excretion.* The decrease in 17-ketosteroid excretion in cirrhosis frequently

... may depend in ... testosterone ...

Water and Salt Metabolism

The liver has an influence on mineral and ... which is probably related ... endocrine effects of this organ This is ... in greater detail in Chapter 64 ... water and salt takes place when the liver is severely damaged The urine ... contains an increased amount of antidiuretic substance which may be related to the antidiuretic hormone of the pituitary gland Increase in adrenal mineral corticoids may also be responsible for the deranged water and salt metabolism (Chapter 64)

Shorr and his group have demonstrated that the liver elaborates and inactivates a vaso depressor principle (VDM) which may be important in the maintenance of normal blood pressure and is present in excessive amounts in irreversible shock In liver disease it is present in excessive amounts and may stimulate the pituitary to excessive secretion of the anti diuretic hormone

Tests Related to Endocrines and Water and Salt Metabolism of the Liver

Urinary Hormone Excretion

The urine in patients with advanced liver disease shows a decrease of 17 ketosteroids and an increase of mineral corticoids and estrogens as compared with the normal The urine in patients with ascites of hepatic origin shows increased amounts of an antidiuretic substance and markedly decreased amounts of sodium (see Chapters 56 and 64)

Sodium and Water Excretion

Sodium and water excretion is impaired sufficiently in liver disease to be detectable by means of clinical laboratory tests The quantity of urine excreted in 24 hours and its sodium content are decreased the spe ... ravity is increased in patients with cirrl ... cially in tho e with ascite

Water Tolerance Test

The water tolerance test is ... follows

1 1500 cc of tap water is administered orally or 1000 cc of 5% glucose in travenously
2 Urine is collected every 30 minutes for five hours
3 The collected specimens are measured
4 The specific gravity and chloride content of each specimen is determined (Adlers berg and Fox)

Normal subjects show a lower specific gravity and higher chloride excretion and all the administered water is excreted in 184 minutes Patients with cirrhosis do not excrete the total amount even by the end of 240 minutes In pa tients with ascites even 50% of administered water is not excreted in 240 minutes (Ralli and associates 1951)

Sodium Excretion Test

Goodyear and associates made use of a sodium excretion test which may have some clinical uses They kept their subjects on a low salt (1 0 gm /day) diet for four days prior to the test After a 12 hour fast the following procedure was carried out

1 500 cc of 5% solution of NaCl was administered slowly (5 cc /min) by the intravenous route
2 No food or water was given during infusion and for 6 to 8 hours after
3 Urine specimens were collected every two hours for eight hours
4 Urine was tested for sodium content and compared with the pretest value

Normal individuals and cirrhotics without *edema or ascites excreted 12 to 54% of the* administered sodium within the period of the test Their urinary sodium increased from 7–82 mEq ... 6–267 mEq per h ... rrhotics with ... tention (ascites ... a) ex crete ... 10% of infused ... nd the urina ... increased fron ... al low valu ... 17 mEq ... 4 6 to 102 ... ter This tes ... some usefu ... fferentiation ... ascites of ci ... f neoplasti

The ... and wate ... in t acute ... nic ph has be ... ate animal improv

monal imbalance as well as the disturbance in the water and salt metabolism is most important in the general clinical picture and complications (discussed in greater detail in Section X) rather than in the diagnosis of liver disease

Blood Volume Regulation

The liver can regulate blood volume by two mechanisms (1) by water retention as discussed above and (2) by circulatory changes within the liver The liver because of its size and rich blood supply has much blood flowing through it and at a given moment a considerable part of the total blood is found in the liver The liver can trap a good deal of blood that enters it and prevent it from reaching the general circulation This can be accomplished by *dilatation of the portal venous channels and* hepatic artery that bring blood to the liver while constricting the outflow channels the hepatic veins This mechanism has been demonstrated and can have a profound effect on the general circulation (Section VIII)

Summary

The functions of the liver are so numerous (over 500) that even a brief discussion of all of them would result in a veritable physiologic encyclopedia Those discussed in this chapter are of clinical importance and are reflected in *clinical laboratory tests* (pages 1-3 and pages 43 47) Other functions of the liver are mentioned throughout the book in pertinent discussions

It is obviou that a clinician cannot hope to test all the functions mentioned here or perform all the tests referred to nor would it be desirable to do so in the usual case However it is useful to utilize a group of tests covering the various spheres of hepatic function These tests should be easy to perform reliable and familiar to the clinician Such a group of liver function tests has been referred to as a *liver profile*

The following group of tests is valuable in the diagnosi differential diagnosis and prognosis of liver disease and they cover several of the functions of the liver

1 Urine bilirubin and urobilinogen
   Serum bilirubin
3 Total serum proteins
   Albumin and globulin fractionation by the $(NH_4)_2SO_4$ (Wolfson Cohn) procedure
4 Flocculation tests
   Cephalin cholesterol flocculation
   Thymol turbidity and flocculation
5 Cholesterol—cholesterol esters
6 Serum alkaline phosphatase
7 Bromsulphalein (5 mg /kg)

To these may be added

8 Intravenous glucose tolerance test
9 Serum cholinesterase determination
10 Prothrombin time and response to vitamin K

Liver function tests vary in their degree of usefulness and applicability depending on their sensitivity Thus some tests may be excessively *sensitive and may give false positive results* while other tests become positive only in advanced hepatic failure or necrosis Among the highly sensitive tests are the flocculation tests (cephalin cholesterol flocculation thymol turbidity and gamma globulin elevation) These may become positive in infections not involving the liver primarily The bromsulphalein clearance test is sensitive but rarely gives false positive reactions The prothrombin time becomes elevated and the antithrombin titer becomes depressed chiefly in advanced progressive liver disease and hence is a sign of poor prognosis Marked serum albumin depression and marked depression of the total as well as esterified cholesterol is also a sign of grave liver disease

Tests even in the same group have slightly different significance All flocculation tests deal with serum proteins abnormalities but in combination yield additional information While their significance may depend largely on globulin elevation they do not necessarily deviate in a parallel fashion Gamma globulin is elevated chiefly in inflammatory diseases of the liver (mesenchymal reaction ?) but may be elevated in nonhepatic disease e g multiple myeloma In this disease the flocculation tests are negative or weakly positive In cirrhosis of the liver the gamma globulin may be significantly elevated while the flocculation tests are weakly positive or negative In post hepatic (obstructive) jaundice flocculation may actually be inhibited even though liver damage has

occurred, and the gamma globulin is elevated The gamma globulin albumin ratio is of prognostic significance

Cholesterol and cholesterol esters may aid in differential diagnosis and the total cholesterol has some prognostic significance The alkaline phosphatase has diagnostic and prognostic significance if correlated with the serum bilirubin and the other tests The bromsulphalein test is valuable in the diagnosis of anicteric portal cirrhosis, the use of the correction table of Zieve and collaborators may make the test useful in icteric cases The intravenous glucose tolerance test and the serum cholinesterase determinations may be helpful in differentiating between hepatic and post hepatic jaundice An increased serum prothrombin time is a sign of poor prognosis and when jaundice is present the response to vitamin K is useful in differential diagnosis

SUMMARY OF LIVER TESTS AND THEIR CLINICAL USEFULNESS

General type	Test	Procedure	Normal Value	Abnormal Value	Clinical Significance and Usefulness
Pigment Metabolism	Bilirubin of serum	Total	1 mg % or less	Above 1 mg %	Hepatocellular damage bile duct obstruction or increased production of bilirubin hemolysis
		1 min prompt	0 25 mg %	Above 0 25 mg %	Hepatocellular damage or bile duct obstruction
		Delayed reacting	less than 1 mg %	Above 1 mg %	If prompt reacting is normal it indicates hemolysis
	Bilirubin of urine	Qualitative	0	+	Hepatocellular damage [illegible] bile duct obstruction
	Bilirubin clearance	1 mg bilirubin per kg I V	Under 5% at 4 hours	Over 5% retained	Sensitive test for hepatocellular damage [illegible] in anicteric patient
	Urobilinogen of urine	Wallace & Diamond	+ 1 10 dil or less	+ 1 20 dil or more	
		2 hr Watson	1 Ehrlich unit or less	Above 1 Ehrlich unit	Hepatocellular damage or increased production of bilirubin = hemolysis
			0 2 mg or less	over 0 2 mg	
		24 hr Quant	3 0 mg or less	Above 3 mg	
	Coproporphyrin — urinary	Total	24 hours under 100 gamma	Above 100 gamma	Hepatocellular damage or bile duct obstruction
		Type I	Under 85 γ	Above 90 γ	Increased in hepatitis
		Type III	40% or less of total	Above 40 γ	Increased in cirrhosis and chronic alcoholism
Excretory Function	B S P	5 mg /kg I V 45 min sample	0 to 4% retention	Above 5%	Sensitive test of hepatocellular damage positive in early mild portal cirrhosis fatty liver and malignant metastasis to liver limited usefulness in jaundiced patients
	Rose bengal	10 cc of [illegible] % sol I V	8 min 55% 16 min 35% or less retained	55% + 35% +	Not as sensitive as the BSP test dye is cheaper and less irritating
Conjugation and Detoxification	Hippuric acid synthesis	Oral 6 gm sod benzoate I V 1 [illegible] gm sod benzoate	3 gm or more in 4 hr urine 0 7 gm or more in 1 hr urine	Below or above normal value	Indicates hepatocellular damage limited usefulness in differential diagnosis of jaundice I V test more accurate renal dysfunction may invalidate test
	Para-aminohippuric (PAH) synthesis	3 gm PAB orally 1 hr blood determination of PAH synthesis	100% synthesis	70% or less	Similar to hippuric acid test but little data available
	Benzoyl glucuronate excretion	5 8 gm Na benzoate orally — [illegible] ingested [illegible] glucuronate 2 4-6 hours	No glucuronate	Glucuronate excreted	Claimed to be more sensitive than hippuric acid test and helpful in differential diagnosis chemical procedure complicated
	Methylation of nicotinamide	Nicotinamide 50 mg orally [illegible] mg I V Methylated comp	Much methylated compound in urine	Methylation impaired	Index of hepatocellular damage but not of clinical importance because of complexity of chemical proce

SUMMARY OF LIVER TESTS AND THEIR CLINICAL USEFULNESS (*Continued*)

Group Test	Test	Procedure	Normal Value	Abnormal Value	Clinical Significance and Usefulness
Carbohydrate Tests ✓	**Glucose tolerance**	**1/3 gm /kg I V**	**Fasting blood sugar in 1 hour**	**Fasting blood sugar 1½ to 2 hours**	**A *useful physiological* test to determine hepatocellular damage may help in differentiation between hepatic and post hepatic jaundice**
	Adrenalin gluconeogenesis	Adrenalin 1 1000 to 0 01 cc per kg I M	Blood sugar rise 40 to 100 mg % at 30 or 60 min	Blood sugar rise less than 40 mg %	*Of special value in glycogen* storage disease where *no* rise in blood sugar occurs abnormal in other types of hepatocellular damage about 60% correlation with other tests
	Insulin tolerance	0 1 u insulin per kg I V	50% fall of blood sugar *in 30 min*utes returns to normal in 90 to 1[illegible]0 min	Hypoglycemia less *marked return* to normal delayed	Test is of physiologic interest *indicates hepatic defect in* COH metabolism defective inactivation of insulin(?) impaired glycogenic effect of insulin(?)
✓	*Galactose* tolerance	Oral 40 gm of galactose	4 hr urine under 3 gm galactose	Over 3 gm galactose	Recommended for differential diagnosis of jaundice galactose is expensive test unreliable because of variability of intestinal absorption and renal excretion
		I V 0 5 gm /kg	Under [illegible]0 mg % galactose in blood at 75 min	Over [illegible]0 mg at 75 min	Eliminates the disadvantages of the oral test sensitive test of parenchymatous damage negative in extrahepatic obstruction value limited by technical complexity (fermentation)
	Lactate clearance	75 mg sodium d lactate/kg I V	0 lactate after 30 min in blood	Above 5 mg % in blood	Of experimental rather than clinical interest
	Pyruvic acid	Determination in blood		Marked elevation in blood and spinal fluid	Interesting from physiological point of view especially elevated in hepatic coma may be of prognostic value
Protein Metabolism	**Gamma Globulin**	**Quantitative electrophoretic or salting out**	**0 7 gm –1 3 gm % or less**	**Above 1 3 gm %**	**Very sensitive shows an elevation in early and mild hepatocellular damage very high in diffuse inflammation of liver hepatitis post hepatitic cirrhosis cholangiolitic cirrhosis increase not so marked in nutritional cirrhosis but may be elevated in other infectious processes and multiple myeloma**
		Turbidity $(NH_4)_2SO_4$ NaCl	**0 to 2 u**	**3 u or above**	
	$ZnSO_4$ turbidity	Tests chiefly γ globul[illegible]tration	4 to 1[illegible] u		High in inflammatory disease of liver inhibited by hyperbilirubinemia and lecithin

SUMMARY OF LIVER TESTS AND THEIR CLINICAL USEFULNESS (*Continued*)

Gen'l Type	Test	Procedure	Normal Value	Abnormal Value	Clinical Significance and Usefulness
Protein Metabolism (*Continued*)	Serum albumin	Electrophoretic salting out	3.2 to 4.4 gm	Under 3.2 gm	Not an early sign of hepatic dysfunction decrease especially when marked is a sign of severe liver disease especially prone to occur in advanced cirrhosis and hepatic necrosis increase of the globulin/albumin ratio is a sign of severe hepatic disease
	Cephalin cholesterol flocculation		0 to 1+ in 48 hours	2+ to 4+ in 48 hours	Flocculation depends on increased globulin and depression and qualitative alteration of albumin sensitive test of active parenchymal disease positive in similar conditions as the gamma globulin may be the first positive test in hepatitis but may be negative in inactive cirrhosis
	Thymol turbidity	30 min turbidity with thymol reagent	0 to 5 u	Over 5 u	Positive test depends on elevation of gamma globulin depression of albumin lipid and lipoprotein elevation highly positive in diffuse inflammatory diseases of liver hepatitis biliary and postnecrotic cirrhosis inhibited by post hepatic jaundice may be negative or only mildly positive in hyperglobulinemias such as multiple myeloma may be slightly positive in nonhepatic inflammations
	Thymol flocculation	18 hr flocculation	0 to 1+	2+ to 4+	Similar but not identical with the thymol turbidity test depends apparently on qualitative change in globulin may remain positive in chronic hepatitis after the turbidity test has become negative

SU\\I\\IARY OF LI\ ER TESTS A\D THEIR CI I\ICAL USEFULNESS (*Contin e I*)

Gene l Typ	*T t*	*P d*	*\ mal l al*	*Ab l l l*	*Cl al S g d U ful*
Carbohydrate Tests	**Glucose tolerance**	**½ gm /kg I **	**Fasting blood sugar in 1 hour**	**Fasting blood sugar 1½ to 2 hours**	**A useful physiological test to determine hepatocellular damage may help in differentiation between hepatic and post hepatic jaundice**
	Adrenal n gl co-neogene	Adrenal n 1 1000 to 0 01 cc per kg I M	Blood sugar r e 40 to 100 mg % at 30 or 60 m n	Blood sugar r se less than 40 mg %	Of spec al value n gl cogen storage d ea e where no ri e in blood sugar occ rs abnormal in other types of hepatocell lar damage about 60% correlat on w h other tests
	Insul n tolerance	0 1 u nsul n per kg I \\	50% fall of blood s gar in 30 m n utes returns to normal n 90 to 0 m n	Hypoglycemia less marked return to normal de la ed	Test is of phys olog c nterest ind cates hepat c defect n COH metabol sm defect e inact vat on of insul n(?) impa red gl cogen c effect of insul n(?)
	Galacto e tolerance	Oral 40 gm of galacto	4 hr ur ne under gm galactose	Over 3 gm galac tose	Recommended for d fferent al d agnos s of jaund ce galac tose is expens ve test un rel able because of ariab l ity of intest nal absorpt on and renal excret on
		I \\ 0 5 gm kg	Under 0 mg % galactose in blood at 75 m n	Over 0 mg at 75 min	El m nates the d sadvantages of the oral test sens t e test of parenchymatous dam age negat ve in extrahepat c obstruct on val e l m ted b techn cal complex ty (fer mentat on)
	Lactate c ea	7 mg sod d lac tate kg I \\	0 lactate after 30 m n in blood	Above 5 mg % in blood	Of experime tal rather tha cl n cal interest
	P r	D t m nat n n bl od		Marked elevat on in blood and sp nal flu d	Interest ng from phys ological point of v ew e pec a l elevated n hepat c coma may be of prognost c value
I rote n Metab l sm	**Gamma Globulin**	**Quantitative electrophoretic or salting out**	**0 7 gm 1 3 gm % or less**	**Above 1 3 gm %**	**Very sensitive shows an elevation in early and mild hepatocellular damage very high in diffuse inflammation of liver hepatitis post hepatitic cirrhosis cholangiolitic cirrhosis increase not so marked in nutritional cirrhos s but may be elevated in other infectious processes and multiple myeloma**
		Turbidity (NH) SO NaCl	**0 to 2 u**	**3 u or above**	
	ZnSO turb d ty	Tests ch efly γ globul n concen t at on	4 to 1 u	Abo e 1 u	H gh in inflammatory d e se of l ver nh b ted b h per b l rub nem a and lec th n

SUMMARY OF LIVER TESTS AND THEIR CLINICAL USEFULNESS (*Continued*)

Group Type	Test	Procedure	Normal Value	Abnormal Value	Clinical Significance and Usefulness
Protein Metabolism (Continued)	✓ Serum albumin	Electrophoretic salting out	3 2 to 4 4 gm	Under 3 2 gm	Not an early sign of hepatic dysfunction decrease especially when marked is a sign of severe liver disease especially prone to occur in advanced cirrhosis and hepatic necrosis increase of the globulin/albumin ratio is a sign of severe hepatic disease
	✓ Cephalin cholesterol flocculation		0 to 1+ in 48 hours	2+ to 4+ in 48 hours	Flocculation depends on increased globulin and depression and qualitative alteration of albumin sensitive test of active parenchymal disease positive in similar conditions as the gamma globulin may be the first positive test in hepatitis but may be negative in inactive cirrhosis
	Thymol turbidity	30 min turbidity with thymol reagent	0 to 5 u	Over 5 u	Positive test depends on elevation of gamma globulin depression of albumin lipid and lipoprotein elevation highly positive in diffuse inflammatory diseases of liver hepatitis biliary and postnecrotic cirrhosis inhibited by post hepatic jaundice may be negative or only mildly positive in hyperglobulinemias such as multiple myeloma may be slightly positive in nonhepatic inflammations
	✓ Thymol flocculation	18 hr flocculation	0 to 1+	2+ to 4+	Similar but not identical with the thymol turbidity test depends apparently on qualitative change in globulin may remain positive in chronic hepatitis after the turbidity test has become negative

SUMMARY OF LIVER TESTS AND THEIR CLINICAL USEFULNESS (*Continued*)

General Type	Test	Procedure	Normal Value	Abnormal Value	Clinical Significance and Usefulness
Carbohydrate Tests	✓ **Glucose tolerance**	**$^1/_3$ gm /kg I V**	**Fasting blood sugar in 1 hour**	**Fasting blood sugar $1^1/_2$ to 2 hours**	**A useful physiological test to determine hepatocellular damage may help in differentiation between hepatic and post hepatic jaundice**
	Adrenalin gluconeogenesis	Adrenalin 1 1000 to 0 01 cc per kg I M	Blood sugar rise 40 to 100 mg % at 30 or 60 min	Blood sugar rise less than 40 mg %	Of special value in glycogen storage disease where no rise in blood sugar occurs abnormal in other types of hepatocellular damage about 60% correlation with other tests
	Insulin tolerance	0 1 u insulin per kg I V	50% fall of blood sugar in 30 minutes returns to normal in 90 to 1 0 min	Hypoglycemia less marked return to normal delayed	Test is of physiologic interest indicates hepatic defect in COH metabolism defective inactivation of insulin(?) impaired glycogenic effect of insulin(?)
	Galactose ✓ tolerance	Oral—40 gm of galact	4 hr urine under 3 gm galactose	Over 3 gm galactose	Recommended for differential diagnosis of jaundice galactose is expensive test unreliable because of variability of intestinal absorption and renal excretion
		I V o gm kg	Under o mg % galactose in blood at 75 min	Over o mg at 75 min	Eliminates the disadvantages of the oral test sensitive test of parenchymatous damage negative in extrahepatic obstruction value limited by technical complexity (fermentation)
	Lactate cle	mg sod d lactat kg I V	o lactate after 30 min in blood	Above 5 mg % in blood	Of experimental rather than clinical interest
	Pyruv	Determination in blood		Marked elevation in blood and spinal fluid	Interesting from physiological point of view especially elevated in hepatic coma may be of prognostic value
Protein Metabolism	**Gamma Globulin**	**Quantitative electrophoretic or salting out**	**0 7 gm -1 3 gm % or less**	**Above 1 3 gm %**	**Very sensitive shows an elevation in early and mild hepatocellular damage very high in diffuse inflammation of liver hepatitis post hepatitic cirrhosis cholangiolitic cirrhosis increase not so marked in nutritional cirrhosis but may be elevated in other infectious processes and multiple myeloma**
		Turbidity (NH) SO_4 NaCl	**0 to 2 u**	**3 u or above**	
	ZnSO turbidity	Tests chiefly γ globulin concentration	4 to 1 u	Above 1 u	High in inflammatory disease of liver inhibited by hyperbilirubinemia and lecithin

SUMMARY OF LIVER TESTS AND THEIR CLINICAL USEFULNESS (Continued)

General Type	Test	Procedure	Normal Value	Abnormal Value	Clinical Significance and Uses
Protein Metabolism (Continued)	✓ Serum albumin	Electrophoretic salting out	3 2 to 4 4 gm	Under 3 2 gm	Not an early sign of hepatic dysfunction decrease especially when marked is a sign of severe liver disease especially prone to occur in advanced cirrhosis and hepatic necrosis increase of the globulin/albumin ratio is a sign of severe hepatic disease
	✓ Cephalin cholesterol flocculation		0 to 1+ in 48 hours	2+ to 4+ in 48 hours	Flocculation depends on increased globulin and depression and qualitative alteration of albumin sensitive test of active parenchymal disease positive in similar conditions as the gamma globulin may be the first positive test in hepatitis but may be negative in inactive cirrhosis
	Thymol turbidity	30 min turbidity with thymol reagent	0 to 5 u	Over 5 u	Positive test depends on elevation of gamma globulin depression of albumin lipid and lipoprotein elevation highly positive in diffuse inflammatory diseases of liver hepatitis biliary and postnecrotic cirrhosis inhibited by post hepatic jaundice may be negative or only mildly positive in hyperglobulinemias such as multiple myeloma may be slightly positive in nonhepatic inflammations
	✓ Thymol flocculation	18 hr flocculation	0 to 1+	2+ to 4+	Similar but not identical with the thymol turbidity test depends apparently on qualitative change in globulin may remain positive in chronic hepatitis after the turbidity test has become negative

General Type	Test	Procedure	Normal Value	Abnormal	Clinical Significance and Usefulness
Protein Metabolism (*Continued*)	18 hour turbidity ratio	Turbidity 18 hrs / Turbidity 30 min	85% or higher	Below 85%	Another way of expressing the thymol turbidity and flocculation; the greater the flocculation the more positive *the test becomes*
	Colloidal gold test		0 to 1+	2 to 4+ or 5+	Sensitive test of hepatocellular damage; depends on elevated globulin and decreased albumin; technically more complicated
	Colloidal red	Flocculation of scarlet red	0 to +	to 4+ or 5+	Less sensitive than other flocculation tests but gives fewer false positives; more likely to be positive in inflammatory diseases of liver
	Amino acid tolerance test	40 cc of 10% protein hydrolysate IV	Fasting level at 35 to 95 min	Fasting level after 95 min	More of experimental than clinical interest
	Prothrombin time	**Undiluted plasma**	**12 to 14 sec**	**Above 15 sec**	**Becomes positive in late and advanced liver disease; hence is more of prognostic than diagnostic importance**
	Vitamin K response	10 to 0 mg IV *or IM*	10 + or more increase in prothrombin in 4 hrs	No increase	In presence of jaundice and prolonged prothrombin time valuable in differentiating between hepatic and posthepatic causes of obstruction
	Vitamin K tolerance test	76 mg vit K IV for 4 successive days	See page 32		Can be done even when prothrombin time is normal and reported as sensitive indicator of hepatic dysfunction; technically is cumbersome because of repeated determinations
	Dicumarol response	00 mg of dicumarol	No prothrombin fall	Fall to 60% of normal	A dangerous test should the prothrombin time get out of hand; dangerous to use dicumarol in patients with hepatic disease
	Antithrombin	Plasma	0 to 25 sec 5 min incubation	Below 0 sec	Antithrombin depressed only in severe progressive hepatic necrosis and decompensation; insensitive test but *important as prognostic sign*
Lipid Metabolism	Lipid Lipid	Quantitative Turbidity	6 to 30 u	Above 30 u	Increased in extrahepatic obstruction, cholangiolitic cirrhosis and fatty liver; normal or decreased in other types of liver disease
	Fat tolerance	*100 gm cottonseed oil orally*	*Serum lipids 65% above fasting at 6 hrs; return to fasting level at 9 hrs*	6 hr rise not so high; 9 hr rise above fasting level	Defect in fat metabolism in liver disease; not a practical test
	Cholesterol	**Total**	**120 to 300 mg %**	**Increased** **Decreased**	**In extrahepatic obstruction, certain types of biliary cirrhosis** **In severe hepatocellular damage**

SUMMARY OF LIVER TESTS AND THEIR CLINICAL USEFULNESS (Co t n ed)

G T p t	T t	P ed	N mal V ue	Abno mal Value	C al S g f ce nd C ulue
Lip d Metabl n (Co t n ed)	Cholesterol (Cont)	Esters	65% or above of total	Decreased	The percentage of cholesterol esters is decreased early in hepatocellular damage may decrease in post hepatic jaundice because of hepatocellular damage but in post hepatic (obstructive) jaundice the % decrease may be due to rise in free cholesterol decrease of both total and esterified cholesterol is serious prognostic sign
E ym and Vitam Te ts	V tamin A	Plasma lev l	40 t 100 micro grams	Decreased	Pr babl nd at defective ab orption although there s als defect ve torag in li er n h pat c njury b rption i mp i ed in b ence of b l n (l tr ct
		Tolerance 180 000 u orally	50% r se ab e fa t ng	No n	
	Alkaline phosphatase	Bodansky King Armstrong Huggins Comori	2 to 4 3 to 13 3 to 15 2 to 4	Increased	In post hepatic jaundice cholangiolitic hepatitis and biliary cirrhosis metastatic neoplasm of liver may be elevated in absence of jaundice and associated with hepatocellular regeneration
				Decreased	If decreased in spite of jaundice or increasing jaundice may be a sign of progressive liver failure and lack of regeneration
	Cholinesterase		0 68 to 1 37 u or 130 to 310 u depending on method	Decreased	Sensitive test of hepatocellular damage remains normal in extra hepatic obstruction hence useful in differential diagnosis may be a sign of impaired protein synthesis in liver

II. The Morphological approach to the Diagnosis of Liver Disease

10

Needle Biopsy of the Liver

The third approach to the diagnosis of liver disease after the clinical and biochemical (or physiological) is the morphological Only a few decades ago most of the morphological data on diseases of the liver was obtained at autopsy and was of no practical importance to the patients involved Biopsy of the liver can be carried out (1) by surgical laparotomy (2) with the aid of the peritoneoscope and (3) by needle The last method has simplified the procedure for both patient and physician and has yielded a wealth of important information

Processes

Surgical biopsy has the advantage of permitting gross inspection and palpation of the liver as well as other intra abdominal organs and a good sized fragment of tissue can be removed However since the tissue thus obtained is usually from the edge of the liver and in close proximity to the gallbladder bed the architecture is not representative of the organ as a whole and may be misleading More over concomitant trauma from surgical procedures may result in round cell infiltration disappearance of liver cells and disruption of reticulum (Keller and Smetana) For this reason needle biopsy has been recommended even when surgical exploration is done The other disadvantages are (1) the extensiveness of the procedure requiring an operating room, (2) the resistance of some surgeons to biopsy of the liver and (3) the risk of poor hemostasis as well as the risk of the laparotomy

Peritoneoscopy with biopsy has some of the advantage as well as disadvantages of the surgical procedure The gross appearance of the liver may be of help in the diagnosis However, a biopsy obtained by the peritoneoscopic biopsy forceps is frequently inadequate and comes only from the surface of the liver For this reason needle biopsy has been used in conjunction with and directed by peritoneoscopy This procedure also requires the use of an operating room and is not without danger Nevertheless peritoneoscopy with biopsy of the liver has been found a useful procedure by some (McHardy et al Keil et al)

Needle biopsy or punch biopsy of the liver is at present the most widely accepted and most useful procedure While its popularity dates back to Iversen and Roholm s publication in 1939 liver puncture for diagnostic purposes was first reported by the Italian investigator Lucatello in 1895 The term aspiration biopsy was first applied to this procedure and still is erroneously used

Instruments

Instruments used for needle biopsy are of the following four types

1. Iversen and Roholm's biopsy trochar (1939)
2. Gillman and Gillman's (1945) biopsy syringe
3. Roth Turkel's biopsy needle (1944)
4. Vim Silverman's biopsy needle (Silverman 1938) and modifications
5. Franseen's trochar similar to Iversen's biopsy trochar

Iversen and Roholm's apparatus consists of a cannula 8 cm long and – mm wide with a sharp ground notched tip This is inserted with a sharp pointed stylet as an obturator The specimen is cut off by rotation of the notched cannula and aspiration with an attached syringe The Franseen trochar is similar to Iversen's trochar but smaller in caliber The Gillmans modified the instrument by making the cannula and obturator an integral part of an especially constructed syringe The obturator is attached to the plunger When the plunger is drawn back the obturator of the needle (cannula) is also withdrawn and a vacuum is formed The vacuum helps to break off and aspirate the biopsy tissue

The Roth Turkel needle which is frequently used in this country consists of (Figure 2) an outer needle with stylet 1 gauge and 7 5 cm long and an adjustable guard and an inner needle with a sharp trephine tip 14 gauge and 5 cm longer than the outer needle The outer needle is inserted through the skin into the substance of the liver the guard is adjusted at the skin the stylet is withdrawn and the inner trephine is inserted to the desired distance past the outer needle This is done with slight rotation finally the trephine is rotated 360 degrees clockwise to cut off completely the portion of tissue A syringe is attached to the inner trephine slight suction is applied and the inner needle is withdrawn The tissue is expressed with the stylet Occasionally the specimen may remain in the outer needle therefore if it is not found in the inner needle suction is applied to the outer needle while it is withdrawn and the specimen expressed with the stylet The above instruments make use of suction so that in a sense these are aspiration biopsies

The Vim Silverman needle is the one most commonly used in this country and makes use of a forceps principle rather than suction in removing the specimen of tissue This needle is preferred because it is the least traumatic and probably the least likely to cause complications This is the needle that I have used almost exclusively Some prefer the Roth Turkel needle because it yields larger specimens of tissue but it is admittedly more dangerous to use The Vim Silverman needle consists of an outer needle 14 gauge and an inner split needle 17 gauge and about 2 cm longer (Fig 3) These needles are made in two lengths with the outer needle either 6 cm or 8 5 cm long and the inner needles – cm longer (Figs 3 and 4) The technique of using this biopsy needle will be described in detail below The inner needle cuts off a column of tissue and the outer needle as it is advanced compresses the two prongs of the inner needle and the tissue within it When the entire instrument is removed the tissue is held firmly in the inner needle

Indications

The usefulness of the procedure has been demonstrated repeatedly both in clinical and experimental medicine The technique is of inestimable help in (1) diagnosis and differential diagnosis of liver disease ( ) as a guide to therapy and determination of usefulness of certain therapeutic agents (3) the study of

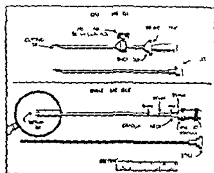


Fig 2 Turkel liver biopsy needle (From Turkel Tph Technique of Bone Marrow Inf s and Tissue B p e th Ed on)

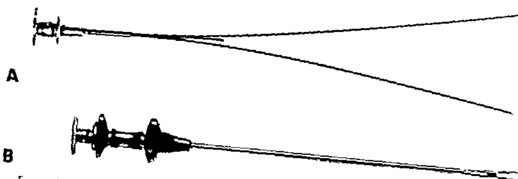


Fig A The split inner needle of the Vim Silverman biopsy needle with the prongs spread apart
B The split inner needle within the outer needle showing how spread to pick up the tissue biopsied

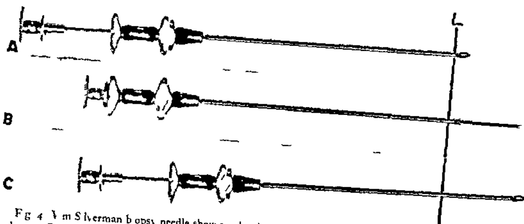


Fig 4 Vim Silverman biopsy needle showing the three positions of the needle in the process of performing a biopsy Position A the needle is entirely hidden in the outer needle when they are inserted assembled into liver L Position B the split needle advanced the outer needle held fixed Position C the outer needle is advanced over the split needle which has picked up a specimen in its jaws

the morphologic evaluation of diseases such as hepatitis and cirrhosis The procedure has been useful in studying the effectiveness of lipotropic agents on the liver lipids in man Our understanding of the pathology of hepatitis has been greatly enhanced by serial liver biopsies during various stages of the disease as well as during convalescence This gives a dynamic viewpoint which cannot be obtained by postmortem studies or single surgical liver biopsies Moreover the fresh and immediately fixed specimens obtained by this means are in many ways superior to autopsy specimens which have undergone postmortem autolysis

As an aid in diagnos psy is indicated in the following sit

1 Differential diagnosis of jaundice
2 Hepatomegaly of undetermined origin
3 Nodular liver of uncertain etiology
4 Splenomegaly of uncertain etiology
5 Upper gastrointestinal hemorrhage possibly due to esophageal varices when the latter are not clearly demonstrated and liver disease is not proved
6 Cases of clinically suspected but unproved liver disease
7 The diagnosis of granulomatous disease of the liver such as sarcoidosis tuberculosis or syphilis may depend on histologic mination (Chapters 72 31 28)
uspected hemochromatosis this procedure may clinch the diagnosis (Chapter

Examples proving these statements are scattered throughout the book. The diagnostic value of this procedure has been demonstrated repeatedly (Table 12).

Contraindications

Contraindications fall into two large categories (1) any condition that may result in hemorrhage and (2) the danger of spreading an infection.

I. *Tendency to hemorrhage*
   A. Increased prothrombin time
   B. Low platelet count
   C. Increased bleeding or coagulation time
   D. Cavernous hemangioma
   E. Severe capillary disease such as scurvy
II. *Danger of infection*
   A. Liver abscess
   B. Suppurative cholangitis
   C. Subphrenic abscess
   D. Right sided empyema (intercostal approach)
   F. Hydatid (Echinococcus) cyst
   I. Diffusely infected skin

A relative contraindication is lack of cooperation by the patient since as will be seen later the cooperation of the patient is required during and after the procedure. This is especially true in the intercostal or transthoracic approach. Some of the above contraindications may also be relative in nature. I have done biopsies repeatedly in patients with a slight elevation of the prothrombin time to 17 seconds (normal 12 to 14) without any untoward effect. Likewise a needle biopsy may be done safely in the face of a slight decrease of thrombocytes, however this procedure should not be done *in the face of disturbed coagulation or bleeding* time. If a needle biopsy is done in the presence of slight abnormality of the prothrombin time and or thrombocytes the indications must outweigh its danger. Certain safeguard must be followed after biopsy is done; if these safeguard cannot be enforced the biopsy is contraindicated.

The removal of some tissue from a cavernous hemangioma may result in intractable hemorrhage. To avoid this one should aspirate with a thin caliber needle before the biopsy needle is inserted. The same precaution may be used

Table 12

Diagnostic Value of Liver Biopsy

Final Diagnosis	No. of Patients	Clinical Diagnosis Incorrect (Biopsy Positive)	Percentage
Cirrhosis	112	20	17.9
Hepatitis	82	12	14.6
Neoplasm of liver	41	4	9.8
Obstructive jaundice	34	7	20.6

Leon Schiff. The Clinical Value of Needle Biopsy of the Liver. Ann. Int. Med. *34* 948 1951.

to avoid the biopsy of an abscess or Echinococcus cyst. If blood or fluid of any type returns biopsy should not be performed. I have inadvertently entered a chronic subphrenic abscess while attempting a liver biopsy through the intercostal approach without untoward results. The procedure proved the diagnosis of subphrenic abscess.

Increased capillary fragility may be difficult to detect except when frank scurvy is present. It should be remembered that increased capillary fragility and permeability may be present in severe liver disease. If a tendency to hemorrhage from nose or other orifices is present then in spite of normal prothrombin coagulation and bleeding time as well as thrombocyte count biopsy should not be attempted.

Some have referred to severe and prolonged obstructive jaundice as a contraindication to liver biopsy because bile peritonitis may result from leakage from a dilated intrahepatic bile duct. Since one of the most important applications of liver biopsy is in the differential diagnosis of jaundice the exclusion of post hepatic or surgical jaundice from the benefit of liver biopsy would sharply curtail its usefulness. However if the biliary tract is so completely obstructed and the jaundice is so severe and progressive that an extrahepatic obstruction is obvious a biopsy is not necessary. That the procedure is not entirely without danger must be admitted and its danger will be elaborated upon later.

Preparation of the Patient

Prior to liver biopsy the patient's history should be taken and a complete physical examination and laboratory tests should be made

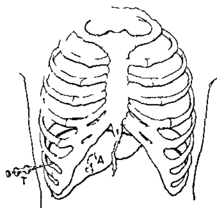


Fig 5 The site of p ncture in needle biopsy of the liver T the trans thoracic or intercostal approach used in small or normal s zed livers A abdominal or subcostal approach used in livers enlarged downward

Liver function tests should be included When the diagnosis is still not clear and indications for liver biopsy are pre ent the possibility of suppurative conditions in and about the liver must be excluded A test of prothrombin time should then be done and it is best to deter mine the bleeding time clotting time and platelet count as well If the results of these tests offer no contraindication to the procedure the biopsy is carried out

Techniques of Liver Biopsy with the Vim Silverman Needle

The patient is given 50 to 75 mg of Demerol (meperidine) hydrochloride subcutaneously 30 minutes before the biopsy is done This pro cedure is most conveniently carried out in the patient s bed The following equipment is *needed*

1 Sterile biopsy needle
2 Small gauge subcutaneous needle and 2 inch needle
3 2 cc and 10 cc syringes
4 1 or 2% procaine
5 Sterile towels
6 Sterile gauze squares
7 Skin disinfectant
8 Scalpel with pointed tip
9 Bottle with formalin for specimen

The approach or *point of puncture* has va with different investigators al terms the approach can be eitl ominal (subcostal) or transth l) I prefer the anterior transabdominal approach in grossly enlarged livers and the transthoracic approach in nonpalpable normal or small livers (Fig 5)

The *transabdominal* approach in enlarged livers is safer than the transthoracic but only if the liver extends three fingerbreadths (6 cm or more) below the right costal margin The Gillmans use the anterior approach inserting the needle into the angle formed by the xiphoid and right lower ribs I make the anterior puncture 2 to 4 cm to the right of the midline just below the costal margin Thus when the liver extends 4 to 6 cm below that point one avoids going through the thin edge of the liver This site of puncture may be varied if there is a nodule on the anterior surface of the liver one should aim for it if a neoplasm is suspected

The ability to obtain a biopsy specimen of a palpable nodule is one of the advantages of the transabdominal approach The other ad vantages are its greater safety from hemor rhage since the needle is not fixed by the ribs and therefore respiration would not tend to tear the liver if hemorrhage does occur it can be readily stopped by laparotomy I have not insisted on the patient s holding his breath in the transabdominal approach

The hazards of the transabdominal approach are (1) perforation of a hollow viscus and (2) *production of peritonitis* however if the sug gestions made above about the selection of patients for this approach and the exact site of puncture are followed complications should rarely be experienced Reports of finding *duodenal and gallbladder mucosa in the biopsy* specimens have appeared but these accidents have not resulted in serious complications I have had no complications with the transab dominal or the transthoracic approach in about 100 biopsies

The *transthor* h is done in the ior or mi line one interspace ow the up of liver dulness This be from 9th interspaces in the or axill and subcutane e are % procaine site c ie infiltra d be s capsule shot the anes

thetizing needle to eliminate penetration into an abscess or hemangioma After anesthetization of the area a small incision is made through the skin with the pointed scalpel The point of the scalpel can be inserted through the subcutaneous tissue and the aponeurosis of the underlying muscle to facilitate the insertion of the biopsy needle The anesthesia and skin incision are carried out in a similar fashion in the subcostal and intercostal approach

As an important safety measure in the transthoracic (intercostal) approach the patient must hold his breath while the biopsy needle is inserted into the liver To facilitate this I instruct the patient to hyperventilate while the preliminaries are being performed The biopsy needle is assembled so that the inner split needle just reaches the level of the outer needle (Figure 4a) The needles are thus inserted into the selected area until the liver is reached when the patient is instructed to exhale and hold his breath The following measures are carried out

1. The entire apparatus is then inserted a short distance (0 5 cm) into the substance of the liver
2. The outer needle is held *stationary* and the inner split needle is inserted completely
3. The inner needle is held stationary while the outer needle is pushed in about cm compressing the column of tissue in the prongs of the inner needle
4. The entire instrument is rotated 360 degrees and removed together (Fig 3) The patient is instructed to resume breathing

When the inner needle is removed from the outer needle and the prongs opened a cylinder of tissue 1 mm in diameter and about cm in length is found This is gently dropped into the formalin for fixation

The entire procedure from insertion of the needle to the removal of the biopsy tissue takes about 15 seconds If the liver is very hard the insertion of the inner cutting needle or the outer needle may be difficult and cause slight delay

Failure to obtain an adequate specimen most frequently depends upon the failure to fix in one position the outer needle while the inner needle is being advanced (point 2) or failure to fix the inner needle while the outer needle is being advanced (point 3) As more experience is acquired these maneuvers are carried out with greater dexterity and fewer failures result If an inadequate specimen is obtained on first trial the needle may be inserted into the same site a second time Failure to obtain an adequate specimen may also occur in massive ascites—the liver may float in the ascitic fluid and be pushed away by the advancing needle or the layer of fluid between the liver and the chest wall may be so deep as to impede the progress of the needle to the liver The *removal of most of the ascitic fluid* before biopsy is attempted is therefore advisable

The patient is instructed to stay in bed for 24 hours after the completion of the biopsy The patient should be watched for hemorrhage by frequent checkups of blood pressure and pulse rate Signs of perforation of hollow viscus—abdominal pain tenderness or rigidity should be watched for carefully The procedure is usually completely painless occasionally a patient complains of slight shoulder pain which may last a few hours

Modifications of the above procedure have been used or proposed The outer needle has been inserted with a stylet through Glisson s capsule when the stylet is removed and the split inner needle is substituted This prolongs the procedure therefore I do not use or recommend it To avoid the common error of failing to fix one of the needles while the other is being advanced Voegtlin devised a modification of the Vim Silverman needle This consists of a side arm and set screws to fix one of the needles while the other is being advanced Nelson (1958) further modified Voegtlin s modification Additional operations lengthen the time of the procedure during which the patient has to hold his breath although this disadvantage is obviated by Nelson s modification Experience usually makes these modifications unnecessary

To avoid hemorrhage

1 Do not use the intercostal approach in a patient who cannot hold his breath
2 Determine bleeding coagulation and prothrombin time and platelet count preoperatively
3 Avoid entering the porta hepatica
4 Aspirate with a small calibre needle along the path of the biopsy needle to avoid entering a large vessel
5 Absolute bed rest and frequent check up of blood pressure and pulse rate postbiopsy
6 Prompt administration of blood if shock occurs and laparotomy if bleeding continues

Bile peritonitis next to hemorrhage is the most serious complication Two of the deaths reported since 1947 were due to this (Hoffman and Rosenthal 1950 Rubenstone et al 1952) Both of these fatalities resulted from perforation of a dilated intrahepatic bile duct in patients with common duct obstruction In this group of patients liver biopsy may help to solve an otherwise insolvable diagnostic problem therefore their exclusion from this procedure would be regrettable To eliminate these accidents it is suggested that biopsies be done earlier before dilatation of intrahepatic ducts become extensive and that an aspirating needle be used preliminary to the biopsy needle thus avoiding the tearing of a bile radical with the biopsy needle

A death from bile embolism to the lungs was recently reported by Brown and Walsh The patient was a 69 year-old man with complete obstruction of the common bile duct due to carcinoma of the ampulla of Vater A communication was apparently formed between a dilated intrahepatic bile duct and a hepatic vein A Franseen needle was used transthoracically This is another hazard of biopsy in complete post hepatic biliary obstruction

Summary—Needle Biopsy

Preparation of Patient

1 Thorough clinical evaluation of patient
2 Rehearsal with patient especially about holding breath
3 Prothrombin time } done day prior to procedure
4 Bleeding time }
5 Platelet count }
6 Demerol 50 to 75 mg
7 Procaine infiltration of skin and subcutaneous tissue

Approach

I Subcostal—transabdominal (only in grossly enlarged livers)
  A Exact site
    1 Two to 4 cm to right of xiphoid just subcostally
    2 Over palpable nodule
  B Advantages
    1 Breath holding is not vitally necessary
    2 Less danger from hemorrhage
    3 Hemorrhage more easily controlled if it occurs
    4 Can aim for a liver nodule
  C Disadvantages
    1 Perforation of hollow viscus possible
    2 Cannot be carried out in small livers

II Intercostal—transthoracic—(in small livers)
  A Exact site
    1 Anterior or midaxillary line
    2 One intercostal space below the upper level of liver dullness
  B Advantages
    1 Can be performed in small or normal livers
    2 Danger of perforation of hollow viscus is negligible
  C Disadvantages
    1 Patient must hold breath
    2 Only very cooperative patients can be used for this approach
    3 Danger of hemorrhage is greater
    4 Surgical treatment of hemorrhage more difficult

COMPLICATIONS

While this procedure is not without risk, the danger of the procedure is decreasing as will be seen from the subsequent statistics The risk is decreased with the experience of the physician and the strict observance of the contraindications and post biopsy care

Minor complications are (1) mild pneumothorax (2) neural a at ite of puncture and (3) diaphragmatic pain These are infrequent and disappear spontaneously without treatment

The [illegible] ip [illegible] t on [illegible] infection (2) an [illegible] b l [illegible] (4) bile pe to [illegible]

I te [illegible] hnique [illegible] l ver [illegible] tion [illegible] a l ver [illegible] careful [illegible] it on [illegible] r linary

[illegible] P

				[illegible] mbe f B p s
Davi al	Subcostal	1946	0	68
Hoffbauer	Subcostal	1947	0	80
Popp et al	Subcostal	1948	0	111
Buck	Sub intercostal	1948	1	56
Koch & Karl	Subcostal	1948	0	100+
Terry	Subcostal	1949	0	7
Kinsell et al	Subcostal	1949	0	100
Levy et al	Subcostal	1949	0	5[illegible]
Popper et al	Intercostal	1949	[illegible]	2 1
Maxwell et al		1950	0	75
Hoffman & Rosenthal	Intercostal	1950	1	75
Moyer & Wurl	Inter and sub-costal	1951	1	00
White et al		1951	0	30
Schiff et al	Intercostal	19 1	0	700
Rubenstone et al	Intercostal	195	1	?
Spellberg et al	Sub and inter costal	195	0	100
Schwartz et al		195	1	500
Molle & Kaplan	Intercostal	195	2	401
Total			7	944

To these can be added 73 patient without a death (Christ an Tyor & Cayer De champs & Steer)

needle at the site of puncture may help to eliminate entering a hepatic abscess Peritonitis from perforation of hollow viscus in the anterior approach is a possibility Hoffbrauer cites one death in this country from generalized peritonitis from perforation of the colon Following all the precautions outlined before should help to avoid such tragedies

Air embolus has been mentioned as a hazard but I am not aware of any deaths reported from this cause

Hemorrhage is the most serious complication and the most frequent cause of death Schiff mentions a mortality from this procedure of 0 5%, but there was not one in over 700 biopsies done by his group Hoffbauer presented a statistical resume of reported deaths up to 1947 There were 12 deaths in 1,350 biopsies which is almost 1% However most of the deaths occurred in early experiences There were five deaths among 289 biopsies up to 1939 while from 1943 to 1946 there were five deaths in over 1 000 biopsies Two other deaths were not correlated with the number of biopsies done Terry reviewed 9 469 [illegible] biopsies in 1949 and found among them seven deaths or a mortality rate of 0 08%

I have reviewed the mortality from biopsies of the liver during the period 1946 to 195 and the picture is even more optimistic Among 2 944 biopsies including over 100 done by my associate and myself there were only seven reported deaths or one death in over 400 biopsies (less than 0 23%) (Table 13) Granted that some deaths escaped publication * or more unfavorable series were not published the procedure still seems to be a relatively safe one It must also be remembered that it is frequently done in very ill patients

The reduction of the mortality from hemorrhage keeping in mind the contraindications depends on avoiding the factors that contribute to it and prompt treatment if bleeding occurs Hemorrhage may result from (1) tearing the liver (2) hemorrhagic diathesis (3) tearing of an intercostal artery or vein or (4) perforation of a portal vessel

* An unpublished fatality from hemorrhage came to my attention in which the hemorrhage was attributable to the perforation of a dilated intrahepatic portal radical

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    4 Surgical treatment of hemorrhage more difficult

5 Small pneumothorax may be produced

Postoperative Care

1 Absolute bed rest for 24 hours
2 Watch for shock check pulse and blood pressure every hour
3 Watch for signs of perforation of viscus
   a abdominal pain
   b severe abdominal tenderness
   c rigidity
4 A source of blood for blood transfusion should be readily available

II — *Pathological Peculiarities—Accuracy of Liver Biopsy*

It has been repeatedly emphasized by various observers but especially by Popper that liver biopsy material differs from post *mortem material* and a reorientation of our conceptions of the morbid pathology of the liver may be in order The relationship between information obtained from liver biopsy as compared to postmortem study of the organ is analogous to the observation of a living stomach through the gastroscope and the *inspection of this organ after surgical extirpation* In the one case, one has the advantage of inspecting a living organ or one as close to the living state as possible in the other case there is more opportunity for inspection but the organ may have undergone marked changes The living or intact cells and structures are more representative of the true morphology than the dead structures which the pathologist usually deals with Popper (1950) has pointed out that certain changes in postmortem liver specimens are due to agonal changes and others to autolysis while the biopsy specimen is fixed immediately and does not show such artefacts He also points out that the widened tissue spaces or spaces of Disse that are so frequently seen in postmortem specimens are not observed in biopsy material and are due to agonal changes

On the other hand the small size of the specimen introduces a problem in interpretation and orientation which requires experience The question may also be raised Is this minute specimen representative of the liver as a whole? In diffuse involvement of the liver such as occurs in cirrhosis hepatitis and fatty metamorphosis the biopsy should pick up the characteristic lesion however it was demonstrated by Waldstein and Szanto who obtained biopsy specimens from different regions of the same liver *that variations in the degree* of fibrosis and inflammatory infiltration occur *in the different specimens Occasionally* in cirrhosis the dense fibrous tissue may resist and deflect the needle so that the column of tissue obtained fails to show fibrosis (Sherlock 1945 Volwiler and Jones 1947) (Fig 6) This is a quantitative rather than a qualitative difference The discrepancies in the grading of liver cell injury were few Good correlation between autopsy and biopsy material was also obtained by Giesen and co workers

The accuracy of liver biopsy in focal lesions such as granulomas of sarcoidosis undulant fever and tuberculosis * is not as great as in the diffuse lesions mentioned but because of their widespread *involvement the fragment of tis*sue will usually show the tubercles on careful

* The tubercle bacillus has been cultured from the liver by Rumball and Baum



Fig. 6. A. Needle biopsy of liver (× 100) showing normal architecture.

B. Surgical biopsy of liver (× 100) 2 weeks later showing large bands of fibrous tissue, bile duct reduplication (left side of picture), distortion of lobular architecture, degeneration of liver cells. Probably post-necrotic cirrhosis. The patient had a massive haemorrhage from varicose veins of the fundus of the stomach (p. 51).

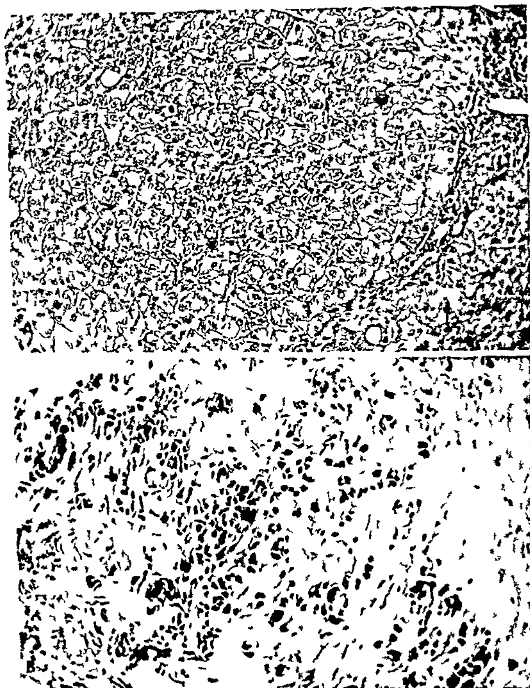


Fig 7 Needle biopsy of liver (X 100) showing infiltration with leukemic cells Chronic lymphatic leukemia no hepatic symptoms

search Indeed this group of lesions can frequently be diagnosed on the basis of the liver biopsy Leukemic infiltrations of the liver may also be discovered on liver biopsy (Fig 7)

Tumors of the liver both primary and secondary can be conclusively diagnosed if the tissue removed contains neoplastic cells However a negative biopsy in suspected neoplasms does not rule them out because they can be easily missed In such cases repeated biopsies may have to be done I have obtained a positive specimen on subsequent biopsies when the first one was negative for tumor (Fig 8) In this type of lesion an attempt should be made to make the puncture over a palpable nodule This is the most certain method of differentiating between a primary carcinoma of the liver and metastatic carcinoma (Fig 9) However occasionally the hepatoma cells may be difficult to distinguish on biopsy from the regenerating nodule of cirrhosis

The liver biopsy may be of considerable and sometimes of critical importance in the differential diagnosis between hepatic (medical) and post hepatic (surgical) jaundice The difficulty of differentiating between infectious hepatitis and common duct obstruction on a histologic basis may vary with the stage of the disease Hepatitis may be more easily diagnosed early in the disease when parenchymal cell changes are demonstrable whereas after several weeks the periportal infiltration may be the only abnormality left and cholangitis is erroneously diagnosed In post hepatic (surgical) jaundice of long duration the superimposed liver cell damage at this late stage may confuse the diagnosis However the finding of bile lake (Fig 15) is considered diagnostic of extrahepatic obstruction The bile lake consists of an irregular pool of bile in the midst of an area of necrosis having a feather ap



F 8 A Needle b ps [illegible] × oo n am pa [illegible] w h marked hep enlargement fever d loss weight and h j decrease n be re Serum bilirubi 1 3 mg ooce Alk e phos ph [illegible] B l k n BSI re n on Floccul on e were norm Th biops h owed mild degen change D gno d b
B Need b ps week l r h w d m e carcinoma I tuma w f nd n he l on

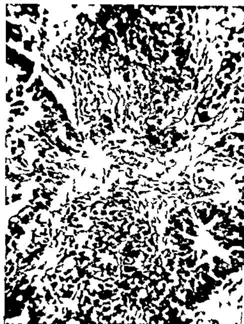


Fig 9 Needle biopsy of liver (X 140) demonstrating metastatic carcinoma This 7 year-old man developed jaundice and hepatomegaly Calculous obstruction of the common bile duct had to be considered Hepatic jaundice was not entirely excluded Liver function tests serum bilirubin 5 3 mg% total protein 6 3 gm albumin 3 2 gm globulin 3 1 gm total cholesterol 15 mg% esters 54% thymol turbidity 6 4 units cephalin cholesterol flocculation 3 plus

pearance It may occur in any portion of the lobule

The importance of needle liver biopsy in clinical medicine is demonstrated by the establishment of a hepatic registry for biopsies by the Armed Forces Institute of Pathology Slides or paraffin embedded specimens may be mailed to the Institute for diagnosis The form used for this purpose along with the classification and diagnostic criteria is reproduced

Classification

List of diagnoses currently used in the Registry of Hepatic Pathology with a brief note regarding the criteria for each

A Cirrhosis
- 1 Portal
- 2 Post necrotic
- 3 Biliary
- 4 Type undetermined (specify most likely)

B Portal fibrosis etiology undetermined
C Fatty metamorphosis (specify slight moderate or marked)
D Active hepatitis
E Toxic hepatitis (specify agent)
F Central *necrosis (etiology undetermined* or specify agent if known)
G Granulomata or granulomatous hepatitis (etiology undetermined or specify agent when demonstrated histologically)
H Bile stasis obstructive type (obstructive jaundice)
I Cholangitis or pericholangitis
J Specific disease where the etiologic agent is demonstrated for example amoebiasis tuberculosis schistosomiasis etc

Criteria

A Cirrhosis

1 *Portal cirrhosis* An increase in the number of small bile ducts and in the amount of portal collagenous tissue with definite pseudolobular formation For practical purposes portal cirrhosis is regarded as a diffuse hepatic disease which involves all of the portal canals in a uniform degree

2 *Postnecrotic cirrhosis* Broad areas of scarring sometimes with an increased number of bile ducts and pseudolobular formation but also showing one or more portal canals which are either within normal limits or are *only slightly altered and which do not enter* into the formation of pseudolobules It is believed that postnecrotic cirrhosis should be employed as a morphologic diagnosis only and should not be interpreted as implying a specific etiology Attempts to differentiate between portal and postnecrotic cirrhosis by means of liver biopsy are uncertain and a high degree of accuracy should not be anticipated

3 *Biliary cirrhosis* An increase in the amount of the portal collagenous tissue and in the number of small bile ducts sometimes with pseudolobule formation but usually with a centrally located efferent vein and small bile thrombi in the centrolobular sinusoids In late stages biliary cirrhosis may become indistinguishable from portal cirrhosis

4 *Undetermined* Those cases of cirrhosis showing pseudolobule formation but which

REGISTRY OF HEPATIC PATHOLOGY
AMERICAN REGISTRY OF PATHOLOGY
ARMED FORCES INSTITUTE OF PATHOLOGY

Washington 25, D. C.

Date

(Mail the completed form with fixed tissue, paraffin blocks or slides to:)

A.F.I.P. Acc. No.
Registry

DIRECTOR, ARMED FORCES INSTITUTE OF PATHOLOGY
WASHINGTON 25, D. C.

PATIENT (full name, address)

Age | *Sex* | *Race* | *Hospital Lab. No.*

CONTRIBUTOR (name & hospital)

HISTORY

PHYSICAL EXAMINATION and LABORATORY FINDINGS

(Over)

(Reverse side)

CLINICAL DIAGNOSES

CONTRIBUTOR'S DIAGNOSES

do not fulfill the criteria for any of the three types outlined above are designated as cirrhosis type undetermined

B Portal Fibrosis Etiology Undetermined

This designation is used for those cases in which there is a rather marked increase in the amount of portal collagenous tissue and sometimes in the number of small bile ducts but *in which pseudolobule formation is not* convincingly demonstrated It may be that some of these cases represent healed biliary cirrhosis but it is also possible that they represent a stage in the pathogenesis of cirrhosis Until this fact is established however it is believed that the term ' early cirrhosis is best avoided

C Fatty Metamorphosis

Whether or not fatty metamorphosis represents a stage in the pathogenesis of all cases of cirrhosis is uncertain For this reason it is coded as a separate entity

D Acute Hepatitis

This term is reserved at the Armed Forces Institute of Pathology for those cases which are presumably of viral origin In addition they may be designated as slight moderate or marked A recent study however has clearly demonstrated that the *degree of histopathologic change is not an accurate index of clinical severity since significant alterations are observed even in clinically mild cases* * Biopsies which have been performed 1 to 6 days after the clinical appearance of jaundice in cases of this disease reveal a marked portal inflammation consisting of mononuclear cells sometimes accompanied by a few eosinophilic leukocytes In addition there is a diffuse scattering of mononuclear cells throughout the lobules usually within the sinusoids Solitary hyaline eosinophilic cells with or without small pyknotic nuclei are usually seen apparently within the sinusoids have been interpreted as necrobiotic liver cells and have been likened to the Councilman bodies of yellow fever The Kupffer cells are prominent and some are distended with a finely granular yellow brown pigment which is believed to be lipochrome derived from necrotic parenchymal cells The histopathologic picture of acute viral hepatitis *apparently changes rather rapidly* and within 2 to 3 weeks the portal and diffuse mononuclear cell reaction resolves except for small aggregates which persist and which may represent foci of necrosis Pigmented Kupffer cells usually remain and may be *quite prominent* Morphologic changes characteristic of chronic viral hepatitis have not been ascertained with certainty

E Toxic Hepatitis

This term is reserved for those cases which show a relatively aseptic acute necrosis of the centrolobular liver cells with very little associated inflammatory reaction Pigmented macrophages in this area are usually prominent The histologic hepatic changes seen in carbon tetrachloride poisoning are a good example of this type of hepatitis

F Central Necrosis

This denotes necrosis of liver cells about efferent veins as seen in hypoxemic condition usually accompanied by infiltrations of polymorphonuclear leukocytes

G Granulomata or Granulomatous Hepatitis

This term is self explanatory The disorder is usually but not necessarily confined to portal areas The etiology is varied

H Bile Stasis Obstructive Type

Small bile thrombi within the sinusoids around the central efferent vein without evidence of inflammation in the portal canals or in the lobules

I Cholangitis or Pericholangitis

This term is reserved for those cases which show an inflammatory reaction confined to the portal canals with little or no inflammation in other parts of the lobules and with bile stasis of the obstructive type

The terms cholangiolitis and cholangiolitic hepatitis have not been used at the Armed Forces Institute of Pathology since the histopathologic criteria necessary for their diagnoses

Italics are authors

are not well understood Suspected case have shown changes which are consistent with those seen in ca es of prolonged viral hepatitis

7 Specific Disease

This of course is self-explanatory

CORRELATION BETWEEN STRUCTURE AND FUNCTION

Needle biop y presented an opportunity for repeated in pection of liver morphology in the living patient and thus stimulated interest in the correlation of structure and function An adequate correlation would eem to be an insurmountable ta k ince the five structural units (1) the parenchymal cells ( ) the Kupffer cells (3) the bile duct cell (4) the vascular channels and (5) the reticulum framework—are respon ible for hundreds of functions and most of these functions reside in the parenchymal cells Nevertheless such correlations have been attempted and are certainly of interest to the clinician

Sherlock attempted a correlation between histologic changes as een in needle biopsy and various biochemical tests in acute hepatitis cirrhosis obstructive jaundice and a mi cella neous group of liver diseases No attempt was made to identify pecific cellular changes but the hepatitis cases were graded according to their severity into A B C and D and the cirrho is into active and inactive Her impres sion from this study was that the height of the serum bilirubin correlated well with the ever ity of the hepatocellular damage The serum albumin decrease correlated well with the degree of damage to parenchymal cell but the alkaline phosphatase was not correlated with hepatocellular damage Thi is at variance with ome other observations which indic ate that the elevated alkaline phosphata e is a sign of regenerative activity Some of the data in the paper seem to show an inverse relation ship between the alkaline pho phata e and the degree of liver damage

Kin ell and co workers in their correlation study looked for degree of activity extent and duration of involvement (chronicity) They regarded the histolo gical sign of *acti ity* as phagocytic cell infiltration and parenchymal cell dam ige such as al normalitie of cell size shape and staining characteristics and multi nucleation The biochemical signs of activity were the cephalin chole terol flocculation the thymol turbidity tests and an elevation of the serum bilirubin

Widespread hepatic damage of long dura tion wa manifested by parenchymal cell damage and fibro is The biochemical charac teri tics of this type of injury were Bromsulpha

TABLE 14

St tistic l R l tion betw en L er F nct on Tests and Patholog c l henomen Witho t R ference to D gnosis

	Diff se l ll d m g	*F l ec*	*R g ne tio*	*Di torted l*	*Per portal f m m l y i ly*	*F tty m l mo pho*	*K pff l i tity*
Ceph lin chol st r l fl cc lat n	+++	o	o	+++	+	o	o
Thymol turb dity	+++	o	++	++	o	o	o
Red cti n of t tal se um prot n	o	o	o	o	o	o	o
Ab orm l serum lb m n gl b l rat o	+++	o	o	o	o	o	+++
Ele at d serum N P N	o	o	o	o	o	o	o
Ele ted r ry ob l n g n	o	o	o	o	o	o	o
Red c d toc l urob l g n	o	o	o	o	o	o	o
Elevated total serum ch le t r l	o	o	o	o	o	o	o
Red ced ch l sterol ester atio	o	o	o	o	o	o	o
Serum bil b el ated bo 8 mg %	+	o	o	o	o	o	+++
Broms lphal n r t nt on	+++	o	o	o	o	o	o
Red ced hippuric ac d y the is	o	o	o	o	o	o	o
Ele at d rum alk lin ph phat	o	o	o	o	o	o	o
Red c d p oth omb n t me pe centag	+	o	o	o	o	o	o
R d c d plasma itam n A	+	o	o	o	o	o	o
Elev ted s d m tat on r t	o	o	o	++	++	o	o

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lein retention diminished hepatic glycogen storage (as detected by their adrenalin test) and elevation of the serum bilirubin Not all their cases studied showed good correlation between the anatomical and biochemical approaches

Norcross and co workers found that elevated serum bilirubin or an elevated alkaline phosphatase was associated with periportal inflammation and fibrosis An elevated serum bilirubin as is to be expected was associated with *bile thrombi and bile duct proliferation* however in many instances they found no correlation between cytological and biochemical changes This lack of correlation between the two approaches has been observed by me as well as by other investigators (Post and Rose 1950 Berk and Shay 1952 Sepulveda et al)

Popper and his group have been keenly interested in correlations between structure and function and have analyzed extensive data along these lines Their observation that diffuse liver cell damage frequently results in alterations in the chemical tests while focal lesions such as abscess and tumors cause no chemical alterations is corroborated by the experience of others Diffuse liver cell damage *showed significant correlation* with Bromsulphalein retention flocculation tests and albumin/globulin ratio alterations There was less correlation with marked elevation of serum bilirubin reduction of plasma vitamin A level and prothrombin time increase No correlation was evident with total protein alkaline phosphatase cholesterol and cholesterol esters Fatty metamorphosis was not well correlated with functional tests (Table 14)

The use of *special stains in bringing out* the basophilic bodies of the cell cytoplasm and their possible relationship to protein synthesis open a provocative approach to this problem Indeed if good correlation between structure and function is to be found it will depend upon refinements in histologic technique that will reveal intracellular chemical changes These basophilic bodies which are stained red with methylgreenpyramin probably consist of pentose nucleic acid These basophilic bodies of the hepatic cells disappear in active cirrhosis and various forms of necrosis In attempting *to correlate this disappearance of* pentose nucleic acid with the defect in synthesis Szanto found a tendency f albumin to be low in instances of b depletion of parenchymal cells

On the other hand the Kupffer histiocytes in viral hepatitis as we cirrhosis are conspicuous containing dance of basophilic bodies These are also characterized by elevated gamma globulin It has therefore b gested that the over activity of these *chymal cells are responsible for increa*thesis of gamma globulin An inc gamma globulin is however not alw related with an increased basophilia cells It has also been suggested that mal function of the liver cells is to gamma globulin and that the injur cells being unable to destroy the globulin allow it to accumulate in e amounts

Theoretically it is attractive to a the increased gamma globulin to meser hyperactivity But it is illogical and dictory *at the same time to attribute t*tive flocculation reactions to parenchy damage since it is generally admitt *the flocculation tests at least in large p* due to the elevation of the gamma glol

The elevated alkaline phosphatase factorily correlated clinically with post obstruction We know however that zyme may be elevated independently of bilirubinemia and there are reliable o tions linking the elevated alkaline phos with hepatic regeneration (p 156) I however was unable to confirm this *needle biopsy studies which makes m*tion the reliability of this approach problem

While the aim to correlate morpholog liver function is one to be strived for it yet obtainable to any considerable One frequently sees instances of definite logic alterations with minimal or questi chemical abnormalities This has recentl re-emphasized by Ricketts The reverse *tion is also encountered For this reaso* biopsy and liver function tests must be u as complementary procedures to sharp diagnostic and research faculties

III The Differential Diagnosis of Jaundice

12

Classification of Jaundice

Introduction

Jaundice while not always present is nevertheless the most conspicuous sign of liver disease It is not only of interest to the physician but has impressed laymen sufficiently to find its way into our language hence the common expression of biliousness and looking at the world through a jaundiced eye

The subject of the differential diagnosis of the causes of jaundice is not just an interesting clinicopathological exercise but is of utmost importance to the physician who attempts to treat this symptom and the patient afflicted with it

It cannot be repeated too often that the satisfactory solution of this puzzle involves the use not only of the laboratory but of all the facilities at our command

1 Clinical including
   (a) painstaking history and
   (b) detailed physical examination
2 Laboratory tests cautiously used and properly interpreted
3 Liver biopsy may be necessary to complete the diagnostic triangle

It may be useful to restate some obvious facts to clarify the problem First jaundice is the clinical manifestation of the discoloration of the skin and mucous membranes from the deposition of abnormal amounts of bilirubin When the blood bilirubin rises above 1 mg *per 100 cc (1 5 mg is regarded by some as the* upper limit of normal) the elastic fibers of the skin and mucous membranes pick up the pigment and when it reaches a sufficient concentration the discoloration becomes evident to the naked eye

What causes jaundice *Actually there is only one cause for jaundice!* All forms of jaundice are due to an *obstruction* or impediment of the flow of pigment from its source of formation to the intestinal tract (Fig 10) The difference depends upon the location and cause of the obstruction For this reason the term obstructive jaundice not only is a misnomer but results in lazy thinking unless the term obstructive is qualified by a designation of location and/or cause

Let us see whether these unorthodox statements will withstand analysis In the normal degradation of hemoglobin bilirubin is formed 1 gm of hemoglobin yielding 40 mg of bilirubin This is formed in the reticuloendothelial system chiefly extrahepatically The bilirubin thus *formed is carried to the liver* which excretes it into the bile duct and it finally reaches the intestines (Figure 12a) Interference

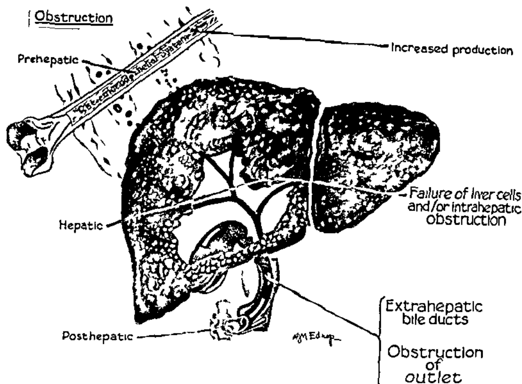


Fig 10 All jaundice is due to obstruction along pathway from source of production of bilirubin to gastro intestinal tract

anywhere along this pathway may result in the drawing back of the bilirubin and its retention in the blood

Thus if there is an overproduction of bilirubin as in hemolytic anemias the liver is unable to excrete the added load and bilirubin accumulates in the blood Here the obstruction is prehepatic and due to prehepatic causes This type of obstruction is analogous to the obstruction that occurs on a two lane highway when traffic from a four lane is suddenly diverted into it The resulting traffic jam is just as much an obstruction as *if a road block* were present

The next location of the obstruction is in the liver resulting in hepatic jaundice In this situation the normal amount of bilirubin is formed but the bilirubin is not excreted as rapidly as it is formed because of liver cell (Kupffer cell) damage and/or obstruction of the intrahepatic bile duct

The last road block to the outflow of bile is *post hepatic* The extrahepatic bile ducts may be blocked by a variety of pathologic processes which will be enumerated later Perhaps the reason the term obstructive jaundice is ordinarily used in reference to the post hepatic type of jaundice is the predominance of mechanical factors in this type of jaundice while in the other two chemical factors are usually more important

Various Classifications of Jaundice

Too many classifications like too many therapeutic agents for a single disease suggest *that none of them is quite satisfactory More* over too many classifications are confusing whereas the only usefulness of classification is to clarify Figure 11 tries to correlate the most important classifications

These different classifications approach the problem from different points of view and stress different phases of the problem Thus 1 the *therapeutic division* into surgical and medical jaundice stresses the most important problem that confronts the clinician who under takes the care of a jaundiced patient The pa

tient s life may depend upon the proper answer to the question Does this jaundiced patient require surgery or is surgery contraindicated and will medical treatment suffice? While this classification may lack scientific value or the subtler implication of the other classification its practical importance is so great that I subordinated the other classification to it (Fig 11)

The *anatomic approach* emphasizes the *location* of the defect that resulted in the icterus As I pointed out before it localizes the level of the obstruction The prehepatic and hepatic jaundice is to be treated only by medical means and therefore is medical jaundice while the post hepatic need surgical intervention and is surgical jaundice The classification of jaundice into prehepatic hepatic and post hepatic has been stressed by Ducci

3 The *physiologic approach* is involved in two different classifications They both refer to disturbed physiology but while one stresses the dysfunction responsible for the hyperbilirubinemia the other stresses the manner of return of the bilirubin to the blood A modification of McNee s classification into hemolytic hepatocellular and obstructive jaundice emphasized the disturbed physiology involved in its production the hemolytic and hepatocellular jaundice being medical while the obstructive (extrahepatic bile ducts) is surgical Rich s classification of retention and regurgitation jaundice emphasizes the nature and level of disturbance of bilirubin circulation and the manner in which the bilirubin is returned to the blood In *retention jaundice* the bilirubin is not even excreted but is retained by the liver cells either because too much bilirubin is formed as in hemolytic states or because the liver cells are damaged and therefore are unable to excrete the normally formed bilirubin The retention jaundice is therefore a medical type of jaundice In *regurgitation jaundice* the bilirubin reaches the bile ducts that is it is excreted by the liver cell but regurgitates or dams back into the blood stream because of an obstruction in the biliary ducts Regurgitation jaundice is therefore chiefly surgical

The difficulty with all the classifications is that in clinical practice they frequently overlap or since more than one factor may be involved in its production a particular case of jaundice will fall into two groups at once An example of this situation is the hemolytic syndrome in which the disturbance is primarily prehepatic owing to increased production of bilirubin but the resultant anemia and increased demand on the liver from the increased pigment production results in hepatocellular damage therefore the jaundice is not simply prehepatic (hemolytic) but hepatic as well Indeed it is possible that most cases of hemolytic jaundice have a hepatocellular factor for a normal liver can get rid of enormous amounts of bilirubin

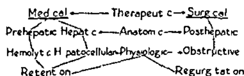
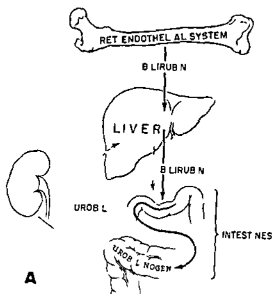
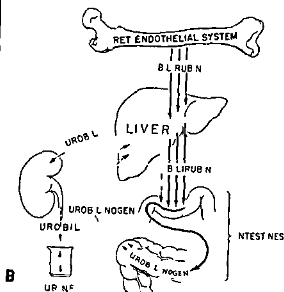


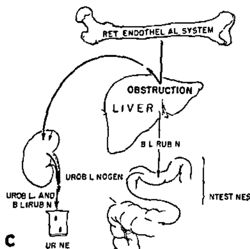
Fig 11 System of classification

At this point the jaundice is still medical but if the increased production of bilirubin over a long period of time results in the formation of biliary calculi these in turn may obstruct the common bile duct and produce post hepatic obstructive jaundice Thus one patient may have prehepatic hepatic and post hepatic jaundice both surgical and medical While this is an extreme example overlapping of lesser degree is an almost constant feature and further complicates the differential diagnosis of the various types of jaundice

In post hepatic jaundice of several weeks duration hepatocellular damage (biliary hepatitis) develops and the jaundice is no longer post hepatic but hepatic as well On the other hand in hepatic jaundice the hyperbilirubinemia is due to the inability of the damaged hepatic cells to excrete the bilirubin as well as to compression of intrahepatic ducts from edema and inflammatory exudates or leakage of bile from damaged bile duct epithelium Thus the jaundice is both hepatocellular and obstructive (intrahepatic) retention and regurgitation







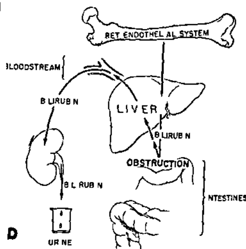


Fig. 12 A schematic presentation of the circulation of the bile pigments. Solid lines represent bilirubin and broken lines represent urobilinogen. Urobilinogen is generally thought not to be excreted as such by the normal liver. (Jankelson, Gastroenterol. *3*: 9, 1946)

A. Normal. The bilirubin is formed in the reticuloendothelial system, excreted by the liver into the intestines, converted in the colon into urobilinogen. Part of this is reabsorbed into the blood stream and re-excreted by the liver. No bilirubin and very little urobilinogen appear in the urine.

B. Prehepatic (hemolytic) jaundice. Excessive amounts of bilirubin are formed, much urobilinogen is formed in the colon. This is reabsorbed. The liver is unable to re-excrete all of this urobilinogen and some of this is excreted in the urine.

C. Hepatic jaundice. The obstruction is in the liver and is usually incomplete. Therefore some bilirubin is shunted back into the blood stream and is excreted by the kidneys. Part of the reabsorbed urobilinogen is likewise excreted by the kidneys.

D. Post hepatic jaundice. The post hepatic obstruction is complete. No bilirubin enters the intestines, no urobilinogen is formed. The regurgitated bilirubin is excreted in part by the kidneys.

TABLE 15

Bile Pigments in Blood, Urine and Feces as an Aid in the Differential Diagnosis of Jaundice

Source	Pigment	Type of Jaundice: Prehepatic	Hepatic	Posthepatic
Blood	Bilirubin	Indirect increased	Prompt reacting increased over 50% of total	Prompt reacting increased over 70% of total
Feces	Urobilinogen	Very high (500–1500 mg/24 hrs.)	Normal or below (100 mg or less)	Absent or very low (5 mg/24 hours)
Urine	Bilirubin	Absent	Present	Present
	Urobilinogen	High (over 5 mg/24 hrs.)	High (over 3 mg/24 hrs.)	Absent or very low (less than 3 mg/24 hrs.)

ENTEROHEPATIC CIRCULATION OF BILE PIGMENTS AND THEIR EXCRETION IN THE URINE AND FECES

Normal

An understanding of enterohepatic circulation of bile pigments and their excretion in the urine and feces in the normal and jaundiced individual is essential for the understanding and differentiation of the various type of jaundice. The bilirubin excreted by the normal liver is changed in the intestinal tract into urobilinogen by bacterial action. The quantity of urobilinogen in a 24 hour stool in a normal person is 40 to 280 mg. Some of this urobilinogen is reabsorbed, returned to the liver via the portal vein and reexcreted in the bile. The excretion of urobilinogen by the normal liver is so efficient that very little of this pigment is normally excreted in urine, less than 3 mg. for 24 hours. With the use of semiquantitative procedure, the Ehrlich reagent gives only a faint pink color in a 1:10 dilution of the urine (Fig. 12a, Table 15).

Prehepatic (Hemolytic) Jaundice

These relationships are disturbed in a characteristic manner in the different types of jaundice. In the prehepatic or hemolytic jaundice, the bilirubin production increases from a normal of 220 mg. to as much as 1500 mg. per day. This results in a corresponding increase in urobilinogen excretion in the stools. The stool urobilinogen may be over 1500 mg per 24 hours (Crosby and Akelroyd, 1952). This increased urobilinogen in the intestines results in increased absorption, and larger amounts of urobilinogen as well as bilirubin are delivered to the liver for excretion. If the liver is unable to excrete the increased amount of urobilinogen, its blood concentration increases and it is excreted by the kidneys (Fig. 12b). Therefore, there is an increased amount of urobilinogen in the urine as well as the feces. An increased amount of urobilinogen in the feces as well as urine is indicative of a hemolytic process.

The other characteristic of this type of jaundice is in regard to the type of hyperbilirubinemia and absence of bilirubinuria. This jaundice is purely the retention type, that is, the bilirubin globin (the indirect reacting) reaches the cells of the liver in such quantities that only a part of the pigment is changed to the direct reacting pigment and excreted. The pigment not handled by the liver cells remains as bilirubin globin in the blood stream. Therefore, the hyperbilirubinemia is due to the delayed indirect reacting type of bilirubin. The hyperbilirubinemia is usually not marked, and because of the character of the pigment, it is not excreted in the urine, hence the term acholuric jaundice. Therefore, in prehepatic jaundice the urine contains much urobilinogen and no or very little bilirubin. Marked bilirubinuria indicates an added hepatic or posthepatic factor or that the prehepatic nature of the jaundice is erroneous.

Hepatic (Hepatocellular) Jaundice

In this type of jaundice the normal quantity of bilirubin is delivered to the liver, but because of the damaged liver cells and the obstruction and damage to the intrahepatic bile ducts, the bilirubin is not completely excreted into the extrahepatic bile ducts. At the onset this type of jaundice has an element of retention (damage to excretory cells) and regurgita

tion from the obstructed intrahepatic bile ducts Therefore in this type of jaundice there is an increase of both the direct prompt reacting bilirubin and the indirect reacting bilirubin

The stools contain less than the normal amount of urobilinogen and the urine contains bilirubin and increased amounts of urobilinogen (24 hours over 3 mg and semiquantitative Ehrlich reaction in dilution of over 1 20) Occasionally one may encounter an almost complete obstruction to the outflow of bile in the hepatic type of jaundice the stools are acholic and there is an absence of urobilinogen in the urine and the results of pigment studies are similar to those in post hepatic jaundice This situation is usually transient eventually urobilinogen appears in the stools and hyperurobilinogenuria returns The only exception to this is the intrahepatic obstruction occasionally observed from arsphenamine and testosterone (see Chapter 24) which shows no element of hepatocellular damage

In the typical case of hepatic jaundice the *urine* contains bilirubin and increased amounts of urobilinogen (Fig 12c Table 15)

Post Hepatic Jaundice

In this type of jaundice, when the extra hepatic block *is complete and continuous* as occurs in malignant obstruction no urobilinogen is detected in the stools (acholic) The bile regurgitates from the large extrahepatic bile ducts and the blood bilirubin is 70% or more of the direct prompt reacting type The urine contains a large amount of bilirubin but no urobilinogen since no bile reaches the gastro intestinal tract and therefore no urobilinogen is formed (Fig 12d Table 15)

13

Medical Jaundice Clinical and Laboratory Features

Prehepatic Jaundice—(Retention Hemolytic)

Familial Nonhemolytic Icterus

This syndrome which is variously referred to as familial nonhemolytic icterus constitutional hepatic dysfunction simple chronic icterus *chronic intermittent juvenile* jaundice or simple familial cholemia demonstrates among other things the inadequacies of all classifications of jaundice Ducci prefers to include it in the prehepatic jaundice group and creates a nonhemolytic subgroup I think this syndrome belongs more properly in the hepatic group since it is most likely due to a hepatic dysfunction rather than a prehepatic defect The excuse for leaving it in the prehepatic group is that the laboratory features are more *in keeping with this group*

It is an uncommon condition of limited clinical importance except that it may create diagnostic confusion and may be mistaken for hemolytic jaundice as well as serious hepatic disease It may be congenital or acquired usually (but not invariably) a familial history is obtained Males predominated (86%) in Comfort and Hoyne s series

The jaundice may bring the patient to the physician or the icterus may be discovered during an examination while the patient is unaware of it The jaundice is intermittent and may be brought on or aggravated by over

ertion nervous strain constipation dys psia migraine or other mild illness It may difficult to ascertain whether these mild mptoms precede accompany or follow the crease of icterus Thus tiredness may actually llow the increased icterus The important ung is that the e individuals apparently suffer o definite ill effect from their abnormality is compatible with a long normal life and ierefore hould not be confused with more rious disea es

Physical fin lings These are negative except or the icterus There is no hepatic enlargement r tenderness There is no splenomegaly or nemia and the color of stools and urine is ormal

Laboratory fin lings These are distinct and iagnostic While the serum bilirubin may reach airly high levels (10 9 mg % Comfort) this ncrease is entirely due to the indirect reacting raction and there is no increase of the prompt eacting bilirubin The urine does not contain ilirubin nor is the urobilinogen increa ed The feces are normal in color but may contain ubnormal amounts of urobilinogen (Barrie) The blood count shows no reticulocytosis nicrocytosis or spherocytosis and the fragility ests are normal

Li er function tes s These tests are normal with the exception of the bilirubin excretion est Dameshek and Singer found that these patients are unable to excrete injected bilirubin n a normal manner Although this is questioned by other observers (Barrie Ducci) it is gener ally agreed that the syndrome is dependent upon a defect in excretion of bilirubin by the hepatic cells

The normality of the liver cells in other respects is evidenced by the normal liver func tion tests as well as normal histology (Krarup and Roholm Meulengracht Alwall) The fluctuation in jaundice in these patients can be explained on the basis of the normal fluctu ations in red cell destruction

Relation to Other Causes of Jaundice

While there is no evidence whatever that a hemolytic process is involved in this syn drome Comfort and Hoyne noted that in one of their patients hemolytic icterus developed four years after the original observation For this reason these authors suggest that a hemo lytic process cannot entirely be excluded as a possible cause for this syndrome

In the nonfamilial or acquired type of nonhemolytic icterus one must consider the possibility of chronic jaundice which occasion ally follows acute infectious hepatitis Per sistent hyperbilirubinemia may be the only evidence of liver dysfunction The other liver function tests may be normal and there may even be an ab ence of bilirubin in the urine and normal amounts of urobilinogen In my ca e (p 272) a liver biopsy was normal and there was absolutely no other evidence of liver disease Nonhemolytic icterus was strongly con sidered but the definite hepatitis preceding the hyperbilirubinemia and the absence of the trait in other siblings made the diagnosis of nonhemolytic icterus untenable

It is likely that some of the cases in the literature reported as chronic hepatic dys function were actually residuals of hepatitis Occasionally al o a hemolytic syndrome is confused with this di ease although it is pos sible that either hepatitis or a hemolytic syn dome may become superimposed on this benign disease

It has also been suggested that this bilirubin may arise from the breakdown of myohemo globin rather than hemoglobin (Barrie) The tiredness weakness and occasional muscle tremors raise the question of the po sible rela tionship of this defect to familial muscular dystrophy The objection to this theory is that myohemoglobin is rapidly excreted by the kidneys however a renal defect could result in retention of myohemoglobin

Hemolytic Syndromes

Classification

Our interest in this ection is with any disease in which there is an increased destruc tion of red cells with consequent increased production of bilirubin The lifespan of a normal erythrocyte is about 1 0 days this may be decreased to 15 or 0 days in patients with hemolytic diseases The corresponding *hemoglobin destruction rises from the normal*

tion from the obstructed intrahepatic bile ducts Therefore in this type of jaundice there is an increase of both the direct prompt reacting bilirubin and the indirect reacting bilirubin

The stools contain less than the normal amount of urobilinogen and the urine contains bilirubin and increased amounts of urobilinogen (24 hours over 3 mg and semiquantitative Ehrlich reaction in dilution of over 1 20) Occasionally one may encounter an almost complete obstruction to the outflow of bile in the hepatic type of jaundice the stools are acholic and there is an absence of urobilinogen in the urine and the results of pigment studies are similar to those in post hepatic jaundice This situation is usually transient eventually urobilinogen appears in the stools and hyperurobilinogenuria returns The only exception to this is the intrahepatic obstruction occasionally observed from arsphenamine and testosterone (see Chapter 24) which shows no element of hepatocellular damage

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The jaundice may bring the patient to the physician or the icterus may be discovered during an examination while the patient is unaware of it The jaundice is intermittent and may be brought on or aggravated by over

exertion, nervous strain, constipation, dyspepsia, migraine or other mild illness. It may be difficult to ascertain whether these mild symptoms precede, accompany or follow the increase of icterus. Thus tiredness may actually follow the increased icterus. The important thing is that these individuals apparently suffer no definite ill effect from their abnormality. It is compatible with a long normal life and therefore should not be confused with more serious diseases.

Physical findings. These are negative except for the icterus. There is no hepatic enlargement or tenderness. There is no splenomegaly or anemia, and the color of stools and urine is normal.

Laboratory findings. These are distinct and diagnostic. While the serum bilirubin may reach fairly high levels (10.9 mg.%, Comfort), this increase is entirely due to the indirect reacting fraction and there is no increase of the prompt reacting bilirubin. The urine does not contain bilirubin, nor is the urobilinogen increased. The feces are normal in color but may contain subnormal amounts of urobilinogen (Barrie). The blood count shows no reticulocytosis, microcytosis or spherocytosis, and the fragility tests are normal.

Liver function tests. These tests are normal with the exception of the bilirubin excretion test. Dameshek and Singer found that these patients are unable to excrete injected bilirubin in a normal manner. Although this is questioned by other observers (Barrie, Ducci), it is generally agreed that the syndrome is dependent upon a defect in excretion of bilirubin by the hepatic cells.

The normality of the liver cells in other respects is evidenced by the normal liver function tests as well as normal histology (Krarup and Roholm, Meulengracht, Alwall). The fluctuation in jaundice in these patients can be explained on the basis of the normal fluctuations in red cell destruction.

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While there is no evidence whatever that a hemolytic process is involved in this syndrome, Comfort and Hoyne noted that in one of their patients hemolytic icterus developed four years after the original observation. For this reason these authors suggest that a hemolytic process cannot entirely be excluded as a possible cause for this syndrome.

In the nonfamilial or acquired type of nonhemolytic icterus one must consider the possibility of chronic jaundice which occasionally follows acute infectious hepatitis. Persistent hyperbilirubinemia may be the only evidence of liver dysfunction. The other liver function tests may be normal and there may even be an absence of bilirubin in the urine and normal amounts of urobilinogen. In my case (p. [illegible]) a liver biopsy was normal and there was absolutely no other evidence of liver disease. Nonhemolytic icterus was strongly considered, but the definite hepatitis preceding the hyperbilirubinemia and the absence of the trait in other siblings made the diagnosis of nonhemolytic icterus untenable.

It is likely that some of the cases in the literature reported as chronic hepatic dysfunction were actually residual of hepatitis. Occasionally also a hemolytic syndrome is confused with this disease, although it is possible that either hepatitis or a hemolytic syndrome may become superimposed on this benign disease.

It has also been suggested that this bilirubin may arise from the breakdown of myohemoglobin rather than hemoglobin (Barrie). The tiredness, weakness and occasional muscle tremors raise the question of the possible relationship of this defect to familial muscular dystrophy. The objection to this theory is that myohemoglobin is rapidly excreted by the kidneys; however, a renal defect could result in retention of myohemoglobin.

HEMOLYTIC SYNDROMES

Classification

Our interest in this section is with any disease in which there is an increased destruction of red cells with consequent increased production of bilirubin. The lifespan of a normal erythrocyte is about 120 days; this may be decreased to 15 or 20 days in patients with hemolytic diseases. The corresponding hemoglobin destruction rises from the normal

of 6 25 gm per day to 45 gm (Crosby and Akelroyd) The pathologic conditions included here will *not necessarily agree entirely with* the hematologist s conception of hemolytic diseases

For this purpose we can classify hemolytic jaundice (anemia) into the following groups

I Defect of erythrocytes (congenital)
 A Familial or congenital hemolytic jaundice (hereditary spherocytosis)
 B Sickle cell anemia
 C Mediterranean anemia
 D Paroxysmal nocturnal hemoglobinuria (Marchiafava Micheli syndrome)
 E Pernicious anemia
 F Hereditary nonspherocytic hemolytic anemia
II Infectious agents
 A Malaria
 B Oroya fever
 C Bacterial infections and septicemias
  1 Staphylococcus
  2 Streptococcus
  3 Bacillus welchii
  4 Pneumonia
  5 Typhoid fever
  6 Paratyphoid fever
III Exogenous toxins
 A Chemical agents
  1 Lead
  2 Phenylhydrazine
  3 Arsine
  4 Saponin
  5 Methyl chloride
  6 Toluene
  7 Benzene and allied compounds
  8 Trinitrotoluene
  9 Dinitrobenzene
  10 Aniline
  11 Acetanalid
  12 Phenacetin
  13 Sulfonamides
  14 Quinine
  15 Colloidal silver
 B Agents of vegetable and animal origin
  1 Fava bean
  2 Castor bean
  3 Snake venoms
IV Endogenous antibodies—hemo-agglutinins and hemolysins
 A *Iso agglutinins*
  1 Transfusion reactions
  2 Erythroblastosis foetalis
 B Cold hemolysins
  1 Paroxysmal cold hemoglobinuria
 C Lederer s anemia
V Secondary symptomatic group
 A Hodgkin s disease
 B Leukemia
 C Lymphosarcoma
 D Carcinomatosis
 E Dermoid cysts
 F Ovarian cysts
 G Hyperthyroidism
 H Liver disease
VI Hemorrhage into tissue with hemolysis of extravasated blood
 A Purpuras
  1 Thrombocytopenic purpura
  2 Henoch s purpura
  3 Schoenlein s purpura
  4 Symptomatic purpura
 B Pulmonary infarction
 C Diseases accompanied by embolic phenomenon

The chronic forms of hemolytic jaundice are more important in the differential diagnosis than the acute variety In the chronic conditions are included the hemolytic anemias and purpuras These will be discussed in some detail

Familial Hemolytic (Acholuric) Jaundice (Hereditary Spherocytosis)

The congenital defect in the erythrocyte in this disease is demonstrated by its rapid destruction when injected into a normal individual while the normal erythrocyte injected into a patient with this disease has a normal lifespan of 120 days The *defect may lie* in the abnormal (alkali resistant) form of hemoglobin similar to fetal (F type) hemoglobin (Singer and associates) or in the supporting structure of the erythrocyte or both

While the disease is frequently discovered in childhood or infancy it may be so mild as to remain undetected until late adult life Careful questioning usually reveals symptoms of pre

vious attacks. The family history is usually positive. Before the history is accepted as negative, relatives should be examined and studied for this defect. It is almost exclusively seen in the Caucasian race, but several cases have been described in a Negro family by Churg and Rosenbaum.

Physical findings. The icterus is usually not marked and may vary in intensity. Pruritus is absent. The icterus may increase with excessive fatigue, emotional stress, or pregnancy. So-called hemolytic crisis is accompanied by chills, fever, weakness, palpitation, abdominal and back pain and dyspnea, and is usually followed by increased icterus. These crises are generally thought to be due to increased hemolysis.

The physical findings include mild icterus, splenic enlargement and occasionally hepatic enlargement. The spleen may be enormous but is not always enlarged. The liver enlargement is slight in about half the cases. Leg ulcers may be present, or pigmentation from healed ulcers may be noted.

Cholelithiasis is a very frequent complication in congenital hemolytic icterus as well as in other hemolytic anemias. Gallbladder disease is said to occur in as high as 65% of patients suffering from this disease. In a recent study by Bates and Brown, 43% showed cholelithiasis. The incidence of this complication increases with age. The calculi are composed of calcium bilirubinate and are the result of the increased pigment excretion in hemolytic diseases. Their presence complicates the diagnostic problem in the presence of jaundice and they may indeed obstruct the common bile duct and superimpose a posthepatic jaundice upon an originally prehepatic jaundice.

When this occurs, medical jaundice becomes converted into surgical jaundice. Moreover, while the jaundice of familial hemolytic icterus is of the medical type, the primary disease is best treated surgically, namely by splenectomy. This is further proof of the inadequacy of any classification and the confusion that may arise if one loses sight of the principles upon which the classification is based.

Laboratory findings. The hematological features include anemia, which is usually only moderate but may become very severe, especially during a crisis, with the erythrocytes falling to about 1,000,000. It may be assumed that the severity of the anemia varies directly with the icterus, but this is not the case except during a crisis. In the interval, patients with considerable jaundice may show little anemia and vice versa. This may be accepted as evidence that the excretory powers of the liver may be at fault more than the increased hemolysis. So here again the prehepatic jaundice has a hepatic element as well.

Microcytosis is usually found in this type of anemia; however, macrocytosis is frequent when the anemia is very severe. Spherocytosis is another characteristic of the red cells in this disease. Reticulocytosis may be marked, with values as high as 50% or more, but usually 5 to [illegible]0%. The *increased fragility* of the red corpuscles to hypotonic saline solution is another diagnostic feature. Hemolysis may begin at 0.52% to as high as 0.87% and be complete at 0.[illegible]% or higher. The cells also show increased fragility to alkalies, acid, saponin, lysolecithin and cobra venom. Coombs' test is usually negative in hereditary spherocytosis. Low serum cholesterol (70 mg/100 cc) has been reported; this may depend upon an increased demand for cholesterol or faulty synthesis, which suggests a possible hepatic abnormality.

The bile pigment disturbance is similar in all forms of hemolytic icterus and has already been alluded to (Table 15). It consists of (1) moderate elevation of serum bilirubin of the indirect type, ( ) increased urine urobilinogen, (3) absence of bilirubin in the urine and (4) increased stool urobilinogen.

Summary

Congenital defect of erythrocyte
Hemoglobin (alkali resistant)
Stroma defective
Hereditary—familial
Rare in Negroes

It is a concentrate of weak anti-Rh antibodies but not specific for them. It is based on the use of an antihuman globulin serum which will agglutinate sensitized red cells.

Begins in childhood
Symptoms and signs
- **Icterus, mild increases with exertion and fatigue**
- **"Hemolytic crisis"**
  - **chills fever**
  - **abdominal pains backache**
  - **weakness palpitation**
  - **increased anemia and icterus**
- **Spleen usually greatly enlarged**
- **Liver enlargement in 50%, slight**
- **Leg ulcers**
- **Cholelithiasis complication in over 40% of cases**

Laboratory
- **Anemia—mild or severe**
  - **Microcytosis**
  - **Spherocytosis**
  - **Reticulocytosis (5-20%)**
- **Erythrocyte fragility to hypotonic saline increased**
- **Low serum cholesterol**
- ***Bile pigment***
  - **Blood—delayed reacting bilirubin increased**
  - **Urine—Urobilinogen ↑**
    Bilirubin 0
  - **Stools Urobilinogen ↑**

Sickle Cell Anemia

Sickle cell anemia is a particular type of hemolytic anemia dependent upon a congenital and hereditary defect in the red cell which is peculiar to Negroes The hemoglobin in the red cell is likewise resistant to alkali denaturation and has characteristic electrophoretic mobility and has been designated as type S hemoglobin (Singer and co workers)

Clinical features In spite of the chronic anemia and jaundice patients may offer few subjective complaints and evidence of anemia and jaundice may be discovered during an unrelated examination During an exacerbation the patient may complain of weakness prostration pains in extremities and abdominal pain The abdominal pain may be severe accompanied by vomiting and if it is epigastric or in the right upper quadrant of the abdomen may suggest gallbladder disease in view of the accompanying jaundice The abdominal pain may be *of sufficient severity to be confused* with an acute surgical abdominal disease

The jaundice may be difficult to detect clinically because of the pigmentation of the skin and muddy conjunctivae The mucous membrane of the mouth may reveal it most distinctly The accompanying pallor suggests the presence of anemia There may be considerable fever and a shock like picture during attacks Generalized abdominal tenderness and tenderness over the liver may further *mislead the clinician* The liver is *frequently* enlarged while the spleen may actually be smaller than normal in chronic cases but is palpable in a small proportion of patients A friction rub may be auscultated over the splenic area Cardiomegaly tachycardia and murmurs may be present Chronic leg ulcers, punched out over the malleoli are a characteristic finding Bony deformities are also of diagnostic import These consist of saber shins tower shaped skulls kyphosis and scoliosis Cholelithiasis *is also a common sequela which results in* diagnostic confusion (Fig 13)

Laboratory features Hematologic study reveals the presence of anemia which may be severe and usually is of the microcytic type however as in congenital hemolytic icterus it may be macrocytic if the anemia is very severe Reticulocytosis (5–25%) is a frequent feature The final diagnosis depends upon the sickling and other bizarre forms of the red cells that develop when a drop of blood is sealed under a cover slip Sickling in a fresh smear may be insignificant In this disease the erythrocytes show decreased fragility to hypotonic salt solution Coomb s test may be positive

X ray examination of the bones may reveal characteristic changes in the skull—*a ground* glass appearance and later the so called hair on end appearance due to trabecular radiation outward from the inner table of the skull The long bones show varying changes including osteoporosis thinning and thickening of the cortex narrowing and complete obliteration of the marrow cavity

Hemoglobinemia of low grade is invariably found in sickle cell anemia and according to Crosby and Dameshek may be used to dis

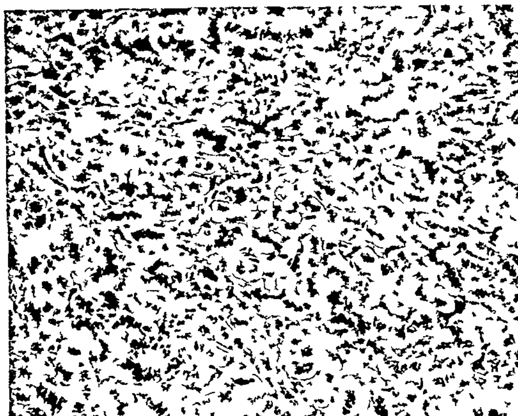


Fig 3 Microscop ct n f need b ps of a l e (X oo of a pa n w h k ce l an m a d ch h (p 7 Show h mos d rnd ps he h pa c e a ed w h l m an b e b a a and d gen a on of h p ce

t ngu h the anem a fro n the s ckle cell tra t Tl s can occur w th ut hem gl l n r a Hemo s lerinuria accompan es the hemoglol nem a Hepat c hen os leros s n a l e demon trated n l er l opsy (F g 13)

Th follow ng ca e den on trates tl e er lapp ng of the var us types of jaun l ce n a g en pat ent An nd v dual who starts out w th a he olyt c syn lrome finally has uper mp ed on tl e prel epat c factor hepat c and po t l epat c factors

Ca e 1

J W 24 ear-ol l Negro male wl o was kn wn t have ckle cell anem a f r many yea entered the hosp tal w th a h tory of recent ep odes of r ght upper abdom nal pa n ch ll fever and pa age of lark ur e and clay-colored st ol

Ph s cal exam nat on revealed a temperature u p to 101°F d st nct scleral an l n uc mem l rane cterus and a tender l er wh cl was palpal le tl ree finge brea lths bel w the costal margin The spleen wa not palpable Scars were note l o er tl e ante or t l al u faces

Exa n nat on of the l lood c nfirm e l the l agn c f s ckle cell anem a The hem glol n was 8 4 gm Tl e erythrocytes numbered 91 m ll n per cul m ll meter an l were pos t ve for s ckl ng The leukoc te c unt was 15 00

The post hepat c nat e f the ja n l ce was confirmed l y the follow ng laboratory data erum l l rul n 6 6 m g 100 cc l l r l nur a ma ked urol l nogen ria moderate thymol tu l d ty 1 1 u flocculat on 0 and cephal n cholesterol flocculat on 0 B l ary calcul were found on ch ecystograpl y An element of hepatocellular abn rmal ty was ested l y

the red count The red count may be normal in the adult type but the other values are always reduced The acute or major type may present many nucleated cells The extreme hypochromia and the red cells having the appearance of an empty circle (target cells) are the characteristic peripheral blood findings The fragility of the erythrocytes is usually decreased The serum iron is increased to the point of saturation and therefore has no free iron binding capacity This is the case in all hemolytic syndromes The evidence of increased bilirubin formation is the same as in the other hemolytic anemias described above

Hemoglobinemia and hemosiderinuria are present in thalassemia major and can be used to differentiate the major from the minor disease

Summary

Thalassemia major (Cooley s anemia)
Children
Thalassemia minor (mild form)
Adults
Hereditary
Mediterranean persons
Clinical features
Depend on type of disease (major or minor)
Systemic symptoms of anemia
Pallor fever
Jaundice mild
Abdominal enlargement due to
Splenomegaly
Hepatomegaly mild
Laboratory features
X ray
Long bones
Thinning of cortex
Medullary cavity increased
Skull *hair-on end appearance*
Anemia
Microcytic
Hypochromic
Target cells
Erythrocyte fragility is decreased
Serum iron is increased
Hemoglobinemia and
Hemosiderinuria in thalassemia major

Paroxysmal Nocturnal Hemoglobinuria with Chronic Hemolytic Anemia (Marchiafa a Micheli Syndrome)

This is a rare disease only 1-3 cases were found in the literature by Crosby up to 1951 Males are more frequently afflicted than females and it occurs most often in the third decade of life The fundamental disorder is in the red cell which results in its easy destruction in the sera of both patients and normal subjects The hemolysis is a continuous process not increased by cold but increased at night

Symptoms These may be mild consisting of weakness fatigability and slight dyspnea or severe and dramatic consisting of chills fever and severe abdominal pain suggestive of a surgical abdominal condition Vomiting hematemesis and melena may also be present The passage of very dark urine in the early morning or at night may be observed by the patient At other times the urine may be normal The outstanding physical findings are the pallor and mild icterus of the skin and mucous membranes and the splenic and hepatic enlargement

The blood plasma and serum are conspicuously discolored assuming a brown color not because of the presence of bilirubin but because of the free hemoglobin Hemoglobinemia may be present even when there is no hemoglobinuria In addition to the normocytic or macrocytic anemia there is reticulocytosis (10- 0%) The fragility of the red cell both mechanical and to hypotonic saline solution is normal

Specific tests Certain tests have been developed to detect the defect in patients with nocturnal hemoglobinuria Apparently these patients have erythrocytes that are unusually *sensitive to the normal thermolabile component* which is present in normal human serum and which increases during sleep One of these tests is the *heat resistance* test of Hegglin and Maier which consists of placing 5 cc of whole blood obtained with special care to prevent hemolysis into an incubator at 37 C for six to twenty four hours Hemolysis visible to the naked eye is a sign of nocturnal hemoglobinuria

The Ham *acid serum test* depends on the

change in pH for the production of hemolysis To avoid the buffering effect of the proteins it has been recommended to defibrinate the blood and to the defibrinated serum 10% by volume of N/5 HCl is added A 50% suspension of washed erythrocytes to be tested is added The volume of this should be 10% of the serum A positive test consists of frank hemolysis This test however is not specific

Another test described by Crosby and Dameshek consists of *activation of the hemolytic factor* in the serum by means of thrombin This test is simple and claimed to be specific

The bile pigment changes are the same as in the other hemolytic anemias but the urine shows hemosiderin containing cells in the sediment when stained with prussian blue in addition to the hemoglobin and urobilinogen

The typical laboratory findings of hemolytic jaundice may be complicated by findings pointing to hepatocellular damage Thrombotic phenomena are a common manifestation hence thrombi in the portal and hepatic veins are frequently observed Central and midzonal hepatic necrosis may be found in addition to the sinusoidal congestion These morphological changes may be reflected in abnormal liver function tests but these are not strongly positive as a rule Simpson and Oldham described a patient showing a thymol turbidity of 10 5 units cephalin cholesterol of 1 plus and Bromsulphalein retention of 7% after 45 minutes

Summary

Rare (123 cases up to 1951)
Males most common
Age third decade
Defect of red cell
Hemolysis increased at night

Symptoms
Weakness fatigability slight dyspnea or chills fever severe abdominal pain

Physical findings
Pallor, mild icterus hepatosplenomegaly
Dark urine at night or early morning

Laboratory findings
Hemoglobinemia with or without
Hemoglobinuria
Hemosiderinuria
Reticulocytosis
Normocytic or macrocytic anemia
Erythrocyte fragility is normal

Diagnostic tests
Heat resistance test
Acid serum test (Ham)
Thrombin activation test (Crosby and Dameshek)

Pernicious Anemia

Pernicious anemia may present itself with slight jaundice superimposed upon the pallor If the patient seeks medical care because of the anemia the pallor is usually marked The other complaints referable to the anemia—tiredness fatigability dyspnea and palpitation—are *among the most annoying Soreness of* the tongue may present itself, or the disease may commence with progressive neurological symptoms The lemon yellowish color so characteristic of pernicious anemia is due to mild icterus The tongue may reveal the typical glossitis of pernicious anemia The atrophy of the papillae give the tongue a smooth glazed appearance The spleen is frequently palpable but not greatly enlarged the liver may also be slightly enlarged but not tender Neurological examination may show impaired vibratory sensation absent or diminished tendon reflexes, ataxia positive Romberg s sign flaccidity or spasticity and sphincter disturbances

Laboratory findings The *absence of free HCl* in the gastric juices with histamine stimulation is practically invariable without which the diagnosis should not be made The peripheral blood shows a *macrocytic hyperchromic anemia* The mean corpuscular volume is above the normal value of 82 to 92 cubic microns and the value for the mean corpuscular hemoglobin is from 33 to 56 $\mu\mu$ (normal 27 to 31 $\mu\mu$) The marked poikilocytosis with the various bizarre forms and the polychromatophilia with the bluish or reddish chromatin particles (Howell Jolly bodies) and acidophilic rings (Cabot s rings) are characteristic findings

The bone marrow findings showing the marked hyperplasia of the erythroid elements with 30 to 50% of these cells nucleated with a preponderance of megaloblasts and the

dramatic response to liver extract or vitamin B_{12} clinch the diagnosis

For the effect of pernicious anemia and other anemias on the liver see page 506

Summary

- Pallor
- Icterus very mild
- Tiredness dyspnea
- Soreness of tongue
- Glossitis palpable spleen
- Liver enlarged occasionally
- Neurological findings

Laboratory findings

- Histamine achlorhydria
- Anemia macrocytic hyperchromic
  - MCV above 92 cubic microns
  - MCH 33 to 56 $\mu\mu$
- Poikilocytosis
- Anisocytosis
- Polychromatophilia
- Bone marrow
  - Megaloblastic hyperplasia
- Response to liver extract or B_{12}

Hereditary Nonspherocytic Hemolytic Jaundice

This disease has all the features of the congenital (hereditary) spherocytosis except that no spherocytosis is present and the red cells show a normal response to hypotonic saline solution The anemia is macrocytic and the spontaneous hemolysis may be due to a defect in the stroma of the erythrocyte Hemoglobinemia has been observed Splenectomy in one patient did not seem to alter the disease Haden observed eight patients in two families

Infectious agents Many infectious agents both protozoal and bacterial can produce hemolytic icterus Indeed this is the commonest type of hemolytic anemia in the world The preponderance of the infectious type of hemolytic jaundice is due to the frequency of malaria in tropical areas The jaundice in malaria is not due entirely to hemolysis the frequency of hepatic injury in this disease is an important factor Details of the relationship of malaria to hepatic injury are discussed in Chapter 33 Here again we have an instance of combined prehepatic and hepatic jaundice The typically recurrent febrile episodes with shaking chills followed by drenching sweats and defervescence and the palpable soft spleen in a patient residing or returning from a tropical or subtropical area make the diagnosis fairly obvious The anemia is usually normocytic but may become slightly macrocytic The leukopenia is another diagnostic feature Finding of the parasites in the blood smear during paroxysms clinches the diagnosis The blood urine and feces pigment findings are similar to those in other types of hemolytic jaundice but the hepatic factor introduces abnormal flocculation tests and other abnormal liver function tests

Oroya fever caused by a flagellated bacillus (Bartanella bacilliformis) encountered in Peru is accompanied by hemolytic anemia and jaundice The disease is transmitted by the sand fly Phlebotomus The symptoms simulate malaria with chills remittent fever headache and muscular pains However the marked leukocytosis and the finding of the organism in the blood smear clarify the diagnosis

Bacterial infections and septicemia of various types may result in hemolytic icterus Septicemias caused by the hemolytic streptococcus and Bacillus welchii infection are among the commonest offenders in this regard however the staphylococcus pneumococcus E coli Eberthella typhi and Salmonella paratyphi can cause hemolysis The specific diseases caused by some of these organisms and bacterial endocarditis and puerperal sepsis may be complicated by the hemolytic jaundice The differential diagnosis should not offer great difficulty since the primary disease precedes the icterus and the clinician's attention is directed toward it However the probable damage to the liver by the systemic infection and pyrexia as well as possible pyogenic abscesses of the liver superimposes a hepatic factor on the prehepatic jaundice (Chapter 5)

Exogenous toxins The various chemical agents listed on page 153 can cause hemolytic jaundice but most of them cause a toxic hepatitis as well (Section V) The toxic action may depend upon the quantity of the noxious agent to which the patient has been exposed or to individual idiosyncrasy The diagnosis depends upon obtaining a history of exposure

to a chemical or demonstrating it in the patient's stomach or excreta. Some of these chemicals, such as trinitrotoluene, dinitrobenzene and methylchloride, are definitely hepatotoxic. The decision as to whether the icterus is due to hemolysis or hepatic injury is based largely on the laboratory findings, but the clinical findings may be of help. Thus, very intense jaundice, severe central nervous system symptoms, marked tenderness and pain over the liver, and marked increase or decrease in size of this organ will point to toxic hepatitis. However, if the pallor is more conspicuous than the jaundice, and the symptoms dependent upon anemia predominate (weakness, dyspnea, palpitation), the hemolytic process is the dominant factor.

In the laboratory sphere, a marked anemia, reticulocytosis with indirect bilirubin in the blood suggests a hemolytic process (prehepatic jaundice), while bilirubinuria and abnormal liver function tests suggest hepatic (damage) jaundice. Some of these toxins produce bone marrow injury with resultant anemia, which further complicates the picture.

Among the *substances of vegetable or animal origin* that cause hemolytic jaundice are the fava bean, the castor bean and certain types of snake venoms. Favism, the disease caused by the fava bean, is discussed in Chapter 23, page 164. This toxin produces hepatic damage as well as hemolysis. The castor bean contains a powerful hemolytic substance—ricin. Some of the snake venoms contain the enzyme lecithinase which converts the lecithin of the erythrocyte into lysolecithin with resulting swelling and rupture of the red cell.

The diagnosis of these hemolytic syndromes is easy when one is cognizant of them and searches for the etiologic agent in the history. Their rarity in most areas of the world brings them only infrequently into the differential diagnosis of jaundice.

Hemolytic Jaundice due to Endogenous Antibodies and Hemolysins—*Transfusion Reaction*

The commonest type of hemolytic jaundice in this group is that due to incompatible blood transfusions. The reaction is usually ushered in with a chill, rise in temperature and backache. The severity of the clinical and laboratory picture varies with the rapidity of the hemolysis. The clinical icterus due to indirect reacting bilirubin may be very mild or quite pronounced. Hyperurobilinogenuria develops and in the more severe cases hemoglobinemia and hemoglobinuria appear. The free hemoglobin is a sign of massive and rapid hemolysis so that there is no time for conversion of the hemoglobin into bilirubin. The massive hemoglobinuria may result in precipitation of hematin in renal tubules, with their subsequent plugging and anuria.

The diagnosis is usually easy because of the sequence of events: the increase of anemia, hemoglobinemia and hemoglobinuria. Hemoglobinemia may be present in the absence of hemoglobinuria. Difficulties in diagnosis arise when the patient is suffering from a disease that may be accompanied by hepatic injury or biliary tract disease. The absence of bilirubinuria and the normal liver function tests and normal alkaline phosphatase would tend to eliminate hepatic and post hepatic jaundice.

Erythroblastosis Foetalis (Icterus Gravis Neonatorum)

Clinical features. Icterus in newborn infants is most commonly due to a hemolytic process. Familial spherocytosis rarely manifests itself in the newborn. Simple icterus neonatorum is a benign self limiting process unaccompanied by severe anemia or hepatosplenomegaly, begins several days after birth, and disappears rapidly without therapy. Icterus gravis neonatorum begins prenatally, and the icterus becomes clinically manifest in first 24 hours. It rarely occurs in the first born, and there is frequently a history of several miscarriages.

The jaundice rapidly progresses and may assume the appearance of a post hepatic icterus. The liver and spleen are enormously enlarged and marked pitting edema may be present. At first there is an increase of urobilinogen in the stool, or this may remain as bilirubin before the bacterial flora of the intestinal tract becomes established. The huge amount of pigment formed may plug the intrahepatic or extrahepatic bile ducts and result in acholic

stools and give the impression of a post hepatic icterus

In some the anemia is the dominant picture and the jaundice is mild This is referred to as congenital anemia of the newborn but the fundamental process is the same as in icterus gravis neonatorum

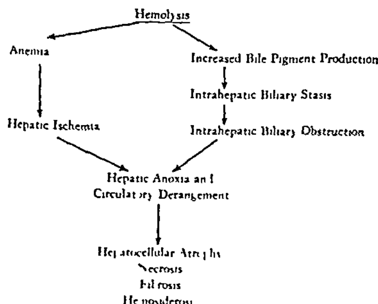
When the jaundice is very marked and the stools become acholic the differentiation from congenital atresia of the bile ducts becomes a problem however in this later condition there is no anemia the splenomegaly is not so prominent a feature and the jaundice becomes marked in the second or third week rather than earlier Skelton and Tovey presented findings suggesting that some cases of congenital atresia of bile ducts may actually be a sequel of erythroblastosis foetalis Permanent obliteration of the bile ducts may follow their plugging with inspissated pigment

Congenital syphilis of the liver is determined by other stigmata of syphilis the positive serology in infant and mother as well as by the absence of characteristic anemia

Hematologic and serologic findings These are crucial in the diagnosis The anemia is usually not marked but there are numerous nucleated red cells (10 000–100 000 nucleated red blood cells per cu mm) in the peripheral blood Marked reticulocytosis macrocytosis and hyperchromia are present Fragility of the erythrocytes to hypertonic saline is normal Blood group determination reveals that these infants and their fathers are Rh positive while the mothers are almost always Rh negative Coomb s test is usually positive

The bile pigment determinations may be confusing in these patients as has been mentioned before The serum bilirubin may become quite high and usually is chiefly of the indirect type however the immediate reacting bilirubin may also increase This may be due to an intrahepatic obstruction of the liver bile ducts and also to hepatocellular damage

Liver damage Anatomical evidence of liver damage has been reported This consists of fibrosis and hemosiderosis as well as focal necrosis Hemosiderosis is of course the most consistent finding Gilmore reports his own experiences with hepatic changes in this disease and cites instances of cirrhosis that followed icterus gravis Craig found various degrees and types of morphologic changes in the liver of 141 erythroblastotic infants studied post mortem These changes included midzonal necrosis fibrosis and regeneration He con



F[illegible] 14 Sch[illegible] [illegible] of the role [illegible] in the pro[illegible] of he[illegible] d[illegible]

cluded that erythroblastosis is a cause of infantile cirrhosis

Biochemical evidence of hepatic damage is the marked depression and even disappearance of cholesterol esters (Rothe Meyer and Hickmans) These patients however showed normal thymol turbidity Cirrhosis or hepatosplenomegaly in infants and children should arouse the suspicion of pre existing erythroblastosis This relationship is supported by the observations of Drummond and Watkins

The pathogenesis of the liver injury is dependent upon a combination of increased demand on the excretory powers of the liver mechanical plugging of the bile canaliculi by viscous bile and the accompanying hypoxia (Fig 14)

Again we find that this disease with primarily prehepatic jaundice becomes complicated by hepatic factors both hepatocellular and hepatocanalicular Nevertheless the disease still remains in the category of medical jaundice

Summary

Clinical

- **History of miscarriages**
- **Not first born**
- **Icterus first 24 hours of life—progressive**
- **Hepatosplenomegaly**
- **Pitting edema**
- **Pallor**

Laboratory

- **Anemia—may be mild**
  - **Nucleated erythrocytes—10 000 to 100 000 per cu mm**
  - **Reticulocytosis**
  - **Macrocytosis**
  - **Hyperchromia**
- **Fragility of erythrocytes normal**
- **Serology**
  - **Wassermann—negative**
  - **Infant and father Rh positive**
  - **Mother Rh negative**
  - **Coomb s test positive**
- **Bile pigments**
  - **Hyperbilirubinemia**
    - **at first indirect delayed reacting type later increase of prompt reacting type**
  - **Stools—increased bile pigment may become acholic from plugged bile ducts**
  - **Urine—Hyperurobilinogenuria bilirubinuria later**
    - **Cholesterol esters decreased or absent**

Liver damage produced by

- **Increased excretory demand**
- **Plugging of bile ducts with viscous bile**
- **Hypoxia—ischemia**

Congenital Familial Nonhemolytic Icterus

Crigler and Najjar studied some cases of icterus neonatorum which was familial but was not dependent upon Rh incompatibility and was nonhemolytic The condition is invariably fatal and accompanied by neurological signs and symptoms (kernicterus) These neurological changes are also components of erythroblastosis foetalis The serum bilirubin rises markedly 10 to 44 mg per 100 cc but the fecal urobilinogen is normal The high serum bilirubin with a normal excretion of pigment by the liver suggests either that the liver has a high threshold for bilirubin excretion or that the bilirubin is of an abnormal type

Paroxysmal (Cold) Hemoglobinuria

This rare disorder is due to a circulating hemolysin which unites with the red cell on exposure to cold The destruction of the red cell occurs when the blood is warmed again It is regarded as a manifestation of syphilis since it is usually seen in individuals with congenital or acquired syphilis It has also been described in nonsyphilitic individuals

Clinical Features A few minutes to several hours after exposure to cold which may actually be mild and seem insignificant the attack begins Generalized aching of abdomen back and legs is followed by vomiting and diarrhea and by a severe chill and a temperature rise up to 104° F The fever is of short duration and is followed by passage of dark brown or almost black urine

Weakness pallor and slight jaundice are apparent The spleen is frequently enlarged and the liver occasionally Evidence of vasomotor disturbances including Raynaud s phe

nomenon may be elicited. Other signs of syphilis may be detected.

Laboratory features. The blood shows a normocytic or macrocytic anemia and reticulocytosis. Spectroscopic examination shows the presence of oxyhemoglobin and methemoglobin and the chemical test for blood is positive.

The specific type of hemolytic process is demonstrated by reproduction of an attack by immersion of two extremities in cold water for 10 to [illegible]0 minutes (Rosenbach test). Immersion of all four extremities may produce dangerous symptoms.

The Donath Landsteiner test for hemolysis following chilling of the blood in vitro is positive. A simplified method of performing this test consists of taking 2 to 3 cc of blood from the patient and from a normal individual and allowing the blood to clot in separate test tubes. The test tubes are then immersed in ice water for 10 minutes, subsequently they are warmed in a water bath at 37 C for 30 minutes. The normal blood shows no hemolysis while blood from a patient with this syndrome shows hemolysis.

Summary

Rare

Circulating hemolysin—activated by cold

Syphilis—congenital or acquired is frequent

Clinical

- **After exposure to cold**
  - **Generalized aching—abdomen back legs**
  - **Chills and temperature rise up to 104 F**
  - **Dark brown or black urine**
  - **Weakness pallor slight jaundice**
  - **Splenomegaly—frequent**
  - **Hepatomegaly—occasionally**
  - **Raynaud's phenomenon**
  - **Signs of syphilis**

Laboratory

- **Anemia**
  - **Normocytic or macrocytic**
- **Reticulocytosis**
- **Rosenbach test**
  - **Chilling of extremities→hemolysis**
- **Donath Landsteiner test**
  - **In vitro chilling of blood→hemolysis**
- **Hemoglobinemia and Hemoglobinuria after exposure to cold**

March Hemoglobinuria

This is a rare benign hemolytic disorder confined almost exclusively to males and usually occurs in the second decade of life. The hemolytic process comes on after strenuous exertion such as prolonged marching or cross country marathon races. The hemolysis is slight and subsides after several hours of rest. Since hyperbilirubinemia which replaces the hemoglobinemia is mild and of short duration it does not present much of a problem in the differential diagnosis of jaundice. No anemia develops in these patients. The diagnosis is based on the history, the normal fragility of the red cells to hypotonic saline and acid, a negative reaction to cold and negative Coombs test.

Lederer's Anemia

In 19[illegible]5 Lederer called attention to an acute hemolytic jaundice occurring in patients suffering from a variety of infections. This syndrome is rapidly cured by a single blood transfusion. Because this anemia occurs secondarily to some type of systemic infection it more properly belongs in the next group to be discussed.

Secondary Symptomatic or Acquired Hemolytic Jaundice

In this group are included hemolytic jaundice occurring in well-defined diseases such as Hodgkin's disease, leukemia, sarcoma, carcinomatosis, dermoid cysts, ovarian cysts, hyperthyroidism and liver disease. It is likely that a hemolysin is responsible for the hemolytic process. The anemia is more likely to be of the macrocytic type. Reticulocytosis is of course also present; however, there is ordinarily no increase in the fragility of the erythrocytes and there is no spherocytosis. There are exceptions to this.

There is an acquired type of hemolytic icterus which is idiopathic and not secondary to infections due to bacteria or toxins or other

cluded that erythroblastosis is a cause of infantile cirrhosis

Biochemical evidence of hepatic damage is the marked depression and even disappearance of cholesterol esters (Rothe Meyer and Hickmans) These patients however showed normal thymol turbidity Cirrhosis or hepatosplenomegaly *in infants and children should arouse* the suspicion of pre existing erythroblastosis This relationship is supported by the observations of Drummond and Watkins

The pathogenesis of the liver injury is dependent upon a combination of increased demand on the excretory powers of the liver mechanical plugging of the bile canaliculi by viscous bile and the accompanying hypoxia (Fig 14)

Again we find that this disease with primarily prehepatic jaundice becomes complicated by hepatic factors both hepatocellular and hepatocanalicular Nevertheless the disease still remains in the category of medical jaundice

Summary

Clinical
- **History of miscarriages**
- **Not first born**
- **Icterus first 24 hours of life—progressive**
- **Hepatosplenomegaly**
- **Pitting edema**
- **Pallor**

Laboratory
- **Anemia—may be mild**
  - **Nucleated erythrocytes—10 000 to 100 000 per cu mm**
  - **Reticulocytosis**
  - **Macrocytosis**
  - **Hyperchromia**
- **Fragility of erythrocytes normal**
- ***Serology***
  - **Wassermann—negative**
  - **Infant and father Rh positive**
  - **Mother, Rh negative**
  - **Coomb s test positive**
- ***Bile pigments***
  - **Hyperbilirubinemia**
    - **at first indirect delayed reacting type later increase of prompt reacting type**
  - **Stools—increased bile pigment may become acholic from plugged bile ducts**
  - **Urine—Hyperurobilinogenuria, bilirubinuria later**
    - **Cholesterol esters decreased or absent**

Liver damage produced by
- **Increased excretory demand**
- **Plugging of bile ducts with viscous bile**
- **Hypoxia—ischemia**

Congenital Familial Nonhemolytic Icterus

Crigler and Najjar studied some cases of icterus neonatorum which was familial but was not dependent upon Rh incompatibility and was nonhemolytic The condition is invariably fatal and accompanied by neurological signs and symptoms (kernicterus) These neurological changes are also components of erythroblastosis foetalis The serum bilirubin rises markedly 10 to 44 mg per 100 cc but the fecal urobilinogen is normal The high serum bilirubin with a normal excretion of pigment by the liver suggests either that the liver has a high threshold for bilirubin excretion or that the bilirubin is of an abnormal type

Paroxysmal (Cold) Hemoglobinuria

This rare disorder is due to a circulating hemolysin which unites with the red cell on exposure to cold The destruction of the red cell occurs when the blood is warmed again It is regarded as a manifestation of syphilis since it is usually seen in individuals with congenital or acquired syphilis It has also been described in nonsyphilitic individuals

Clinical Features A few minutes to several hours after exposure to cold which may actually be mild and seem insignificant the attack begins Generalized aching of abdomen back and legs is followed by vomiting and diarrhea and by a severe chill and a temperature rise up to 104 F The fever is of short duration and is followed by passage of dark brown or almost black urine

Weakness pallor and slight jaundice are apparent The spleen is frequently enlarged and the liver occasionally Evidence of vasomotor disturbances including Raynaud s phe

phenomenon may be elicited. Other signs of syphilis may be detected.

Laboratory features. The blood shows a normocytic or macrocytic anemia and reticulocytosis. Spectroscopic examination shows the presence of oxyhemoglobin and methemoglobin and the chemical test for blood is positive.

The specific type of hemolytic process is demonstrated by reproduction of an attack by immersion of two extremities in cold water for 10 to 30 minutes (Rosenbach test). Immersion of all four extremities may produce dangerous symptoms.

The Donath-Landsteiner test for hemolysis following chilling of the blood in vitro is positive. A simplified method of performing this test consists of taking 10 cc. of blood from the patient and from a normal individual and allowing the blood to clot in separate test tubes. The test tubes are then immersed in ice water for 10 minutes, subsequently they are warmed in a water bath at 37° C. for 30 minutes. The normal blood shows no hemolysis, while blood from a patient with this syndrome shows hemolysis.

Summary

- **Rare**
- **Circulating hemolysin activated by cold**
- **Syphilis congenital or acquired is frequent**

Clinical
- **After exposure to cold**
  - **Generalized aching—abdomen back legs**
  - **Chills and temperature rise up to 104° F**
  - **Dark brown or black urine**
  - **Weakness pallor slight jaundice**
  - **Splenomegaly frequent**
  - **Hepatomegaly occasionally**
  - **Raynaud's phenomenon**
  - **Signs of syphilis**

Laboratory
- **Anemia**
  - **Normocytic or macrocytic**
  - **Reticulocytosis**
- **Rosenbach test**
  - **Chilling of extremities—hemolysis**
- **Donath-Landsteiner test**
  - **In vitro chilling of blood—hemolysis**
- **Hemoglobinemia and**
- **Hemoglobinuria after exposure to cold**

March Hemoglobinuria

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There [illegible] type [illegible] with [illegible] features [illegible] the [illegible].

diseases Dameshek and Schwartz point out that a hemolysin is responsible for the hemolytic process and the source of the hemolysin may be the spleen They note that spherocytosis and increased fragility of erythrocytes to hypotonic saline may be seen in the acquired as well as congenital variety They further indicate that the spherocytosis may be the result of the action of a hemolysin It can be seen then that the acquired form of hemolytic jaundice may be difficult to distinguish from the familial except by the negative family history or unless it is secondary to a well defined disease

The changes in the bile pigments in the blood urine and stools are the same as in other types of hemolytic disease Abnormal liver function tests may be seen in the hemolytic syndromes secondary to diseases that in themselves produce hepatic damage This of course is especially true if a hemolytic anemia occurs secondary to liver disease Some of these primary diseases may produce post hepatic jaundice by compression of extrahepatic bile ducts Among these can be included Hodgkin s disease lymphosarcoma carcinoma and other tumors In such instances the prehepatic (hemolytic) medical jaundice is converted to a surgical jaundice unless the obstructing tumor lymph nodes are responsive to irradiation

Hemolytic Jaundice due to Hemolysis of Extravasated Blood

Purpuras In any disease in which there is appreciable extravasation of blood into the tissues or formation of hemorrhagic infarcts the erythrocytes are hemolyzed and excessive amounts of bilirubin are formed with resultant prehepatic jaundice In the various types of purpuras while the hemorrhagic tendency is most conspicuous jaundice may develop The primary disease can be diagnosed easily by the obvious hemorrhagic manifestations the anemia thrombocytopenia and the increased bleeding time in the idiopathic variety However if hemorrhage occurs into the liver, this organ may become enlarged and tender Even so the laboratory findings should point to the prehepatic origin of the jaundice

Anothe feature complicating the diagnosis is the occasional thrombocytopenia seen in patients with cirrhosis and splenomegaly Other evidence of cirrhosis both clinical and laboratory should dispel the confusion (p 86)

Embolic phenomenon Pulmonary infarctions may result in a mild prehepatic icterus The icterus in patients with congestive heart failure may in part be due to this The hepatic enlargement and tenderness in passive congestion of the liver may suggest primary hepatic disease as the cause and indeed hepatic injury may take place in long standing congestive heart failure (p 488) Splenic enlargement as well as deranged liver function tests would tend to point to intrinsic hepatic disease (hepatic jaundice)

Subacute bacterial endocarditis with extensive embolic phenomena may result in prehepatic jaundice Intravascular bacterial hemolysis may contribute to the hemolytic process Hepatic damage may become superimposed As was pointed out before in any type of prehepatic jaundice some hepatic injury is likely to be present and interfere with the excretory power of the liver so that in the final analysis the important factor is not so much whether there is a hepatic element to the jaundice but rather how much of the icterus is due to hepatic and how much to prehepatic factors This evaluation can usually be made from the clinical picture the pigment findings in blood urine and feces (Table 16) and other liver function tests

Hepatic Jaundice

Classification

THE second large group of medical jaundice is due to intrinsic hepatic disease. It will be discussed here only in general terms, since the diagnosis and differential diagnosis of specific hepatic diseases is taken up in detail throughout the book. As has been mentioned before, hepatic jaundice may be hepatocellular or hepatocanalicular in origin, but it usually is a combination of the two. Particularly the laboratory findings and to a lesser extent the clinical picture vary according to the predominance of one or the other factor. If the hepatocanalicular factor is foremost, the jaundice may be very difficult to distinguish from posthepatic or surgical jaundice. All clinical and laboratory facilities have to be mobilized in order to permit a correct diagnosis, which is crucial for the welfare of the patient.

The following etiologic agents and diseases are involved in the production of hepatic jaundice.

Infectious Agents

Viral
- Infectious hepatitis, homologous serum hepatitis, yellow fever, infectious mononucleosis (?)

Spirochetal
- Weil's disease, syphilis, relapsing fever

Bacterial
- Pyogenic liver abscess, tuberculosis [illegible]
- Liver brucellosis

Protozoal
- Amebic hepatitis and abscess

Metazoal
- Schistosomiasis
- Hepatic d[illegible]
- Hydatid cyst [illegible] liver flukes

Chemical Agents

Phosphorus, chlorinated hydrocarbons, arsenic, cinchophen, organic solvents (See Section [illegible])

Metabolic

- Hyperthyroidism
- Hemochromatosis
- Gaucher's disease
- Niemann-Pick disease
- Amyloid disease
- Glycogen storage disease (Van Creveld-Gierke

Nutritional

- Portal cirrhosis
- Fatty liver
- Hemosiderosis
- Kwashiorkor

Neoplastic

- Cavernous hemangioma
- Primary carcinoma of liver
- Metastatic carcinoma
- Metastatic sarcoma

In[illegible] of Liver

- Lymphomas
- Leukemias

It can be readily [illegible] and [illegible] The [illegible] of posthepatic [illegible] confirm [illegible] open [illegible] the liver [illegible] patient. Thus [illegible] [illegible]

if the abscesses are miliary or multiple only medical treatment could be effective A similar situation may be encountered in tuberculosis of the liver except that surgery would be much more rarely indicated or effective

The same conflict arises in primary hepatomas the jaundice here again is of hepatic origin but some hepatomas can be and have been successfully extirpated and therefore should be included under surgical jaundice The majority of hepatomas however are not amenable to surgery because of their extent

The majority of the diseases producing hepatic jaundice can be treated successfully only by medical means and surgical exploration may be definitely detrimental Among these are the viral hepatitites other infections such as Weil s disease and the cirrhoses The diagnostic generalization will apply to the diseases in this group For salient features of the various types of jaundice see Table 16

History

One may be able to elicit evidence of the use of excessive amounts of alcohol and/or dietary deficiency exposure to toxic agents accidental occupational or suicidal the administration of blood or blood products or other injections 30 to 60 days prior to onset of illness or contact with other cases of jaundice either sporadic or epidemic These may give a clue to the etiologic background of the commonest types of hepatocellular jaundice hepatitis (toxic or viral) and cirrhosis

Symptoms

The symptoms may include nondescript dyspepsia anorexia and mild abdominal pain The anorexia may be of recent origin and accompanied by malaise nausea and vomiting as in viral hepatitis In cirrhosis the anorexia may be of longer duration accompanied by weakness fatigability edema and abdominal enlargement A weight gain with anorexia may point to the water retention of cirrhosis *Abdominal pain* is present in hepatocellular jaundice but is usually mild aching or dragging in nature and localized to the epigastrium or right upper quadrant of the abdomen The pain may be aggravated by motion jarring or the erect position Occasionally the pain may be severe and colicky and may resemble biliary colic Massive hematemesis may precede the jaundice of portal cirrhosis

Physical Findings

The physical findings include hepatic enlargement and tenderness The tenderness is diffuse and is elicited by palpation as well as percussion The tenderness elicited by fist percussion over the right lower portion of the thorax is pathognomonic of viral hepatitis but *unfortunately it is absent occasionally* The liver may be soft as in hepatitis or quite firm or even hard as in cirrhosis but it is never grossly nodular Some irregularity of the surface may be detected in postnecrotic cirrhosis and more rarely in portal cirrhosis Gross nodularity or solitary nodules are indicative of neoplasm of the liver metastatic or primary (For differential diagnosis between these see Chapter 20)

The spleen is enlarged in 10 to 35% of cases in this group i e more frequently than in the post hepatic group and not as frequently as in the prehepatic group In long standing portal cirrhosis with severe portal hypertension the *splenic enlargement may be marked*

Fever may be absent or may be slight This is true in both cirrhosis and hepatitis However in fulminating hepatitis with massive necrosis fever may be high with terminal hyperpyrexia Occasionally in cirrhosis with progressive necrosis fever may be remittent and quite high resembling a septic process

Jaundice may vary widely in intensity from very mild to most intense Itching is usually absent in hepatic jaundice and the jaundice in spite of the intensity has a yellow cast ("yellow jaundice")

Spider nevi and fetor hepaticus when present are pathognomonic of hepatic jaundice *and when present outweigh all other* findings to the contrary Spider nevi are seen most commonly in cirrhosis but may occur in long standing hepatitis metastatic carcinoma of the liver and very rarely in syphilis *of the liver* The sites of predilection are the upper chest neck face and uper extremities (p 403) Fetor

TABLE 16

Complete Clinical and Laboratory Findings in Various Types of Jaundice

HEMOLYTIC
Prehepatic
Retention
History
Familial—occasional
Infections
Toxin
Symptoms
Chill followed by jaundice
Fever
Weakness
Physical Findings
Jaundice
Pallor of mucous membranes
Spleen—almost always enlarged
Liver—smooth, not tender, moderately enlarged
Leg ulcers
Laboratory Findings
Anemia—microcytic, spherocytic, fragility in- cr[eased] and sickling
Marked reticulocytosis
Serum bilirubin—indirect delayed reaction
Urine—high urobilinogen
Hemoglobinuria—may be present
Liver function test — usually normal
Stools—high urobilinogen
Blood—parasites

HEPATOCELLULAR
Hepatic
Retention
Toxic
History
Alcoholism
Dietary deficiency
Exposure to toxic agents
Hypodermic injections
Blood [or] plasma infusions
Contact with other c[a]s[es]
Symptoms
Vague dyspepsia
Anorexia
Abdominal pain—mild right upper quadrant
Jaundice without pruritus
Fever—low grade
Hematemesis
Physical Findings
Liver enlarged—regular or irregular, tender
Spleen—enlarged in 10–35%
Spider nevi, palmar erythema
Fetor hepaticus
Ascites
Laboratory Findings
Blood: anemia—mild at to marked
Stool—urobilinogen may be negative briefly
Urobilinogen—increased
Thymol turbidity—above 5 U.

Thymol flocculation—above 1 plus
Cephalin-cholesterol flocculation—above 1 plus
Albumin—under 3 gm %
Globulin—above 3 gm %
Cholesterol esters—under 65%
Alkaline phosphatase—normal or slightly elevated

OBSTRUCTIVE Regurgitation
Posthepatic
History
Attacks of biliary colic
Selective dyspepsia
Jaundice
Symptoms
Pain—severe colicky, dull aching lumbar pain may be absent
Vomiting and weight loss
Acholic stool
Pruritus
Chill and fever
Physical Findings
Jaundice—skin may be greenish
Gallbladder—may be palpable or not
Liver—may be enlarged
Spleen—usually not enlarged
Palpable mass
Laboratory Findings
Blood—RBC normal or slightly decreased
Reticulocytosis—absent
Leukocytosis—may be marked
Urine—urobilinogen negative, bilirubinuria marked
Stool—urobilinogen negative (acholic), may be positive for blood
Serum bilirubin chiefly direct reacting
Alkaline phosphatase high
Flocculation tests negative early
Serum prothrombin normal
Cholesterol normal or low
Total cholesterol high

hepaticus is an important sign of hepatocellular damage and should be looked for in all cases of jaundice.

The presence of ascites identifies a given jaundice as the hepatic type. The rare exception to this is the ascites produced by peritoneal metastasis when a malignant neoplasm is obstructing the extrahepatic bile ducts.

LABORATORY FEATURES

Laboratory tests are of considerable help in the diagnosis of hepatic jaundice but should be evaluated in conjunction with the clinical data. A normal leukocyte count or leukopenia with a tendency to relative lymphocytosis in a patient with jaundice and fever would suggest hepatitis (hepatic jaundice) rather than

if the abscesses are miliary or multiple only medical treatment could be effective A similar situation may be encountered in tuberculosis of the liver except that surgery would be much more rarely indicated or effective

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TAB E 16

C mp C n al nd Labo a F nd ng n Va ous T pe of Jaund ce

HEMO YTIC
Prehepa c
Re ent n
H tory
Fam a —oc a ion
Infect n
Tox n
Symp m
Ch ll f w d by ja nd e
Fever
Weaknes
Ph al F nd n
Ja nd e
Pallo of m ou m mb nes
Sp een a mo a ways n a ged
Li r—smoo h no nde mod a e arg d
Leg u e
Lab a ory F nd ng
Anem a m roc sph ocy e f agi y n crea d nd s kl ng
Ma ked ocy os s
S m b l rub n ndire d a ed a n
U ne—h gh ob l'nog n
H m glob nuria m b p n
L e func on no ma
Stoo h gh u ob n gen
B ood p as es
H roce AR
Hepa c
Re en on
Tox
H ry
A coho m
D a defi n
Exposu e o tox ag n s
H pod m c nje n
B ood o p a ma nf on
Con a w h h ta es
S mp m
Vague d pep a
An rex
Abd m na p m d righ ppe quad ant
Ja nd w ho pru u
Fe er—low g ade
H ma em s
Ph a F nd ng
I en ged rr gul nde
Sp een e ged n o- %
Spide ne p ma e h m
Fet h p u
A es
Lab at ry F nd
B rub n m m d ma ked
S d r b gen ma be n ga e briefly
Urob nog n ria ncrea ed
Th mol b d h t
Th mol fl ccu a on—abo p us
Cepha n-cho rol f occu a ion—abo e pl
A bum n—und 3 gm %
Globul n abo e gm %
Cho ro es rs—und 65%
A ka ne ph pha a e—n rma or s gh l eva ed
OB TR CTIVE Regu g on
P h p
H y
A acks b a co u
Se d pep a
Jaund
S mpt m
Pain— e e, col k d ach l mbar pain may be b en
Vom ng nd w gh s
Ach c ot
Prurit
Ch and
Ph a F nd
Jaund ce—sk n ma be gre n h
G a b add ma be p ab nd
L m be ged
Sp n n n arged
I pab e mas
Lab a y F nd ng
B ood RBC n ma o gh d a d
R loc tos —ab n
Leukoc os m be ma ked
U ne—u b n gen n ga b rub nu a ma ked
S obil nogen neg a ho e n neopl m pos e or blood
Serum b b n ch fl d rec g
A k l ne phosph a e h gh
Floc a n e g
Serum pro ein n m
Ch ro n m l w
T a h l h gh

hepat s an mpo tant gn of hepato cellular dan age an l sl ou d be looked fo n all cases of jaund ce

The p e ence of a c te den hes a g en jaund e as tl e l epat c t pe The rare excep t on to th s the a c te produced by per toneal meta ta wl en a mal gnant neopla m ol structing the extrahepat b le ducts

LABORATORY FEATURES

Laboratory test are of con derable help n tl e d agno s of hepat c ja nd ce l ut should be e aluated n conjunct n w th the cl n cal data A normal leukoc te count or leukopen a w tl a ten lency to relat ve lymphocytos s n a pat ent w h ja n l ce and fever wo l l sug gest hepat (l ep c j un l ce) rather than

common bile duct obstruction (post hepatic jaundice)

The bile pigments have a particular pattern of distribution in the blood urine and feces (Table 15) The hyperbilirubinemia is composed of over 50% of the direct reacting bilirubin with this bilirubin appears in the urine The stools contain a slightly decreased amount of urobilinogen and the quantitative as well as semiquantitative tests for urobilinogen show an increase of this pigment in the urine The exceptions to this are the cases of intrahepatic biliary obstruction (hepatocanalicular jaundice) Especially in viral hepatitis the intra hepatic biliary obstruction may result in exclusion of bilirubin from the intestine with acholic stools and absence of urobilinogen in the urine This however seldom lasts more than seven days and is preceded and followed by hyperurobilinogenuria If the patient is seen during this phase of his illness the similarity to post hepatic obstruction may be striking and confusing (Chapter 39)

The results of liver function tests that reflect hepatocellular derangement are abnormal in hepatic icterus

1 The serum proteins are altered by decrease in albumin and elevation of the gamma globulin
2 The flocculation tests
   a cephalin cholesterol flocculation
   b thymol turbidity
   c colloidal gold and
   d colloidal red are positive
3 The total cholesterol is variable but the per centage of cholesterol esters is usually decreased
4 Serum cholinesterase is decreased
5 Intravenous glucose tolerance test shows delayed return to fasting level (Chapter 5)

It is imperative to use several liver function tests since even in severe parenchymal liver damage some functions of the liver may remain nearly intact however it is not necessary to use all the tests Not all of the flocculation tests need be used but at least two are advisable The cephalin cholesterol and thymol turbidity tests are the most commonly used The flocculation tests are not invariably positive In addition to the protein tests it is valuable to have one or two tests related to other spheres of hepatic activity namely the cholesterol determination and the cholinesterase or glucose tolerance test

The decrease of serum albumin is a valuable index of hepatic jaundice but is likely to appear only in advanced disease The gamma globulin however rises in early and mild hepatic injury it may be elevated in post hepatic jaundice and therefore is of limited value in differential diagnosis The gamma globulin is especially high in inflammatory diseases of the liver such as hepatitis or post necrotic cirrhosis and less elevated in portal cirrhosis

Although the flocculation tests depend in large measure on the decrease of albumin and elevation of gamma globulin other less clearly defined factors are involved as well It has been pointed out by various observers notably by Ducci that the flocculation tests may remain negative in post hepatic jaundice even when the gamma globulin is elevated hence they are valuable in differentiating between hepatic and post hepatic jaundice The flocculation tests and especially the thymol turbidity, are more strongly positive in inflammatory diseases of the liver such as hepatitis than in nutritional liver diseases such as portal cirrhosis In general the cephalin cholesterol may be more sensitive than the thymol turbidity test but the flocculation tests do not show parallel deviation In infectious hepatitis the chephalin cholesterol test is the first to become abnormal but the thymol turbidity and flocculation may remain positive later in convalescence

The serum or plasma cholesterol and cholesterol esters may be of some value in the differential diagnosis of jaundice, but are not nearly as useful as the flocculation test In order that these may be of most value the total and esterified cholesterol should be determined It should be recalled that plasma cholesterol may deviate from the normal even in prehepatic jaundice In congenital hemolytic icterus the total cholesterol is depressed and in erythroblastosis foetalis the cholesterol esters may be markedly decreased or even absent

The drop in cholesterol esters below 65% has been considered suggestive of hepatocellular dysfunction because of the importance of the liver in cholesterol esterification. However, I have frequently seen a depression of cholesterol esters in post-hepatic jaundice. This has also been pointed out by others (Portis, King and Taubenhaus). The drop in cholesterol esters in post-hepatic jaundice may be the earliest indication of hepatocellular injury and is observed in the presence of otherwise normal liver function tests. The relative decrease in cholesterol esters in post-hepatic jaundice may be deceptive since in this type of jaundice there is frequently a rise in the total cholesterol. If the total cholesterol rises while the esters remain at the same absolute level, the decrease in ester percentage may be startling. This phenomenon was demonstrated in experimental animals by ligation of the common duct (p. 34).

This apparent but not real decrease of the esters may be difficult to prove in a given case because of the accepted variation of the normal total cholesterol values and the lack of data in most instances on the cholesterol value before jaundice occurred. For instance, a given individual may normally have a total cholesterol of 130 mg % and esters of 90 mg % or 69% of the total cholesterol. These values are quite normal. Post-hepatic jaundice develops with a total cholesterol of 290 mg %. The esters are still 90 mg %, but this is only 31% of the total cholesterol and therefore quite abnormal. Now, in the absence of the values before the individual became jaundiced, one would naturally surmise that there had been a drop in the cholesterol esters, but actually the absolute value of the cholesterol esters remained the same, but the total cholesterol (free cholesterol) rose. This phenomenon was observed in experimental post-hepatic jaundice.

In hepatic jaundice there is usually an absolute drop in cholesterol esters with no rise or an actual drop of total cholesterol as well (Table 17). Indeed, a marked drop of cholesterol esters to nearly zero is almost always a sign of hepatic jaundice. This is also true of a marked drop in total cholesterol. Therefore the diagnostic pattern for this test in hepatic jaundice is a drop or low total cholesterol and marked decrease of cholesterol esters; however, in many cases of hepatic icterus such clear-cut values are not obtained. The most glaring exception to the rule about cholesterol values in hepatic jaundice is biliary cirrhosis, especially the variety referred to as xanthomatous biliary cirrhosis (Chapter 59). In this condition the total cholesterol is markedly elevated. While the percentage of esters is reduced, the absolute value of the cholesterol esters is as high as in normal persons. As parenchymatous damage increases, the total cholesterol as well as the ester fraction decreases to levels seen in other types of hepatic jaundice.

TABLE 17

Serum Cholesterol and Cholesterol Ester Values in Hepatic and Post-Hepatic Jaundice

	Hepatic Jaundice	*Post-Hepatic Jaundice*
Cholesterol	Normal or decreased	Increased
Esters		
Absolute value	Decreased	Normal
Percentage	Decreased	Decreased

The serum *cholinesterase* values are low in hepatocellular jaundice and may be of assistance in differential diagnosis. Its value is questioned by Sborov and Keller. Althausen regards the intravenous galactose tolerance test as a reliable test for this differentiation. Seventy-five minutes after the intravenous injection of 1 cc. of 50% galactose per kilogram of body weight, more than [illegible] mg % of this sugar remains in the peripheral blood in parenchymatous jaundice. A prolonged prothrombin time which does not respond to intravenous injection of vitamin K is a sign of hepatic jaundice.

The alkaline phosphatase may be normal or slightly elevated in parenchymatous jaundice. As a rule, the elevation of this enzyme is not as marked in hepatic as in post-hepatic jaundice. Usually this enzyme does not go above 10 Bodansky units, but because of many exceptions the alkaline phosphatase by itself cannot be regarded as a reliable differential between the two forms of jaundice.

Intense jaundice with a slight or no elevation of the alkaline phosphatase is definitely diagnostic of hepatic jaundice During convalescence with decreasing icterus the alkaline phosphatase may remain elevated or rise indicating parenchymatous regeneration (Chapter 8)

These tests follow the pattern outlined in hepatic jaundice with marked hepatocellular involvement however if the involvement is chiefly hepatocanalicular (intrahepatic biliary obstruction) the tests of hepatic function may be normal while the pigment excretion (acholic stools) and high alkaline phosphatase may suggest post hepatic jaundice Indeed, the differentiation between hepatic (hepatocanalicular) and post hepatic biliary obstruction may be a most difficult and at times an unsolvable problem short of surgical exploration

In most cases of hepatic jaundice there is a factor of intrahepatic biliary obstruction but it is usually not sufficient to confuse the diagnosis In viral hepatitis the involvement may be predominantly related to the bile ducts with relatively little parenchymal involvement i e the periportal exudation process may be most marked and the parenchymal necrosis mild or nearly absent The process may be more in the nature of cholangiolitis rather than hepatitis (cholangiolitic hepatitis) In any case the cholangiolitic process may predominate for a while and produce complete intrahepatic biliary obstruction If the parenchymal changes are mild and the tests of hepatic function remain relatively normal the picture becomes highly suggestive of post hepatic jaundice The complete obstruction is usually of short duration—about seven days The important fact to keep in mind is that in viral hepatitis the liver function tests may not reveal a clear picture of hepatic jaundice—in some during a short phase of the disease and in others throughout the disease In such instances one must depend more on symptoms physical findings the leukocyte count and liver biopsy

Moreover certain drugs may produce a toxic hepatitis with predominantly intrahepatic bile duct involvement among these are (1) arsphenamine (2) testosterone (3) thiouracil and (4) sulfonamides (Ducci Chapter 24) In these cases liver function tests may be normal but there is complete exclusion of bile from the intestines and therefore no urobilinogen in the urine

A history of administration of one of these drugs should aid in diagnosis In cases of hepatitis a history of exposure to other cases or human blood products the absence of colic and the presence of percussion tenderness over the liver and a palpable spleen should also strengthen the diagnosis of hepatic jaundice

TABLE 18
Histologic Lesions of Viral Hepatitis and Obstructive Jaundice

Lesion	Hepatitis	Obstructive Jaundice
Universal triaditis	+++	o to +
Portal area inflammation	+++	± to ++
Character of exudate	Lymph mono eos	Lymph poly mono
Intralobular exudate	± to +++	o to +
Bile duct dilatation	o	+
Bile duct proliferation	o to +	± to ++
Cholangitis	o	± to ++
Ductular epithelial artefact	o to +	± to ++
Major bile duct stasis	o	o to ++
Canalicular stasis	± to ++	++ to +++
Intracellular stasis	± to +	++ to +++
Kupffer cell pigmentation	+ to ++	++ to +++
Focal intralobular necrosis	+ to +++	o to ±
Focal cellular hyalinization	++	o
Fatty vacuolization	o	o to +
Feathery degeneration	o	o to ++
Bile lake	o	o to ++
Balloon cells	+ to +++	o
Shrunken cells	+ to +++	o to ±
Nuclear abnormality	++	o
Mitotic figures	o to ++	o to ±
Multiple nuclei	++ to +++	o to ±
Irregularity of cell cord	± to +++	o to +
Portal area fibrosis	o to ±	o to ++

From F G Weisbrod et al Needle Biopsy of the Liver III Experiences in the Differential Diagnosis of Jaundice Gastroenterology *14* 1 1950

Liver Biopsy

Needle liver biopsy should be of definite help in this difficult differentiation (Chapter 11) The finding of a bile lake would clinch the diagnosis of post hepatic obstruction (Fig 15) Parenchymal cell involvement such as necrosis hyalinization nuclear abnormalities and cytoplasmic abnormalities is usually found only in hepatitis while dilatation stasis and thrombi of larger bile ducts are signs of post hepatic jaundice (see Table 18) Schiff and his group also emphasize the exudative process in the portal triads (triaditis) in hepatitis and the balloon or shrunken parenchymatous cells The exudative process in post hepatic obstruction consists chiefly of polymorphonuclear cells while in hepatitis lymphocytes are mainly involved Thus it should be possible with composite data to differentiate between intra and extrahepatic biliary obstruction in most cases



Fig 15 Microscopic picture of bile lake in a patient with post hepatic jaundice Note the pool of extravasated bile in the center of a larger area of degenerated liver cells (From Leon Schiff *Liver Injury* Ninth Conference 19 0 Josiah Macy Jr Foundation New York N Y p 41)

15

Surgical Jaundice (Post-Hepatic Jaundice)

Features Common to this Group

JAUNDICE that is amenable to surgical therapy is chiefly of the post hepatic type (obstructive regurgitation jaundice) and results from a mechanical obstruction of the extrahepatic bile duct especially the common bile duct

The various factors causing extrahepatic bile duct obstruction or post hepatic surgical jaundice may be classified as follows

I Calculi
- A Biliary
- B Pancreatic

II Neoplasms
- A Type
  1. Carcinoma
  2. Sarcoma
  3. Adenoma
  4. *Cysts*
- B Site of origin
  1. Gallbladder
  2. Cystic duct
  3. Common bile duct
  4. Papilla of Vater
  5. Duodenum
  6. Pancreas
  7. Liver

III Lymph node enlargement
  A Metastatic carcinoma
  B Hodgkin s disease
  C Lymphosarcoma
  D Leukemia
  E Tuberculosis
  F Syphilis
IV Scars (stenosis fibrosis)
  A Extrinsic with reference to duct
  B Intrinsic with reference to duct
  C Spontaneous due to inflammation
  D Postoperative or other trauma
V Inflammatory lesions
  A Edema
  B Abscess formation
VI Parasitic
  A Ascariasis
  B Hepatic distomiasis
  C Strongyloidiasis
  D Echinococciasis

Factors Responsible for Post Hepatic Jaundice May also Produce Hepatic Jaundice

Again it should be noted that some of the etiologic factors listed as responsible for post hepatic obstructive jaundice may also be responsible for hepatic jaundice depending upon the exact site and mechanism of their action The only exception to this crossing over of classification line is calculi in group I Primarily calculi can produce only jaundice of the post hepatic type but eventually all of the factors including calculi may result in the introduction of a hepatic factor In group II any of the neoplasms may metastasize to the liver and produce jaundice of the hepatic type this is especially true of primary malignant tumors of the liver But in spite of hepatic involvement by the neoplasm the primary cause of the jaundice may be pressure on extrahepatic bile ducts

In case of involvement by Hodgkin s disease lymphosarcomas leukemias tuberculosis and syphilis of nodes situated in the porta hepatica or adjacent to the common duct the jaundice would obviously be of the post hepatic type But any of these diseases may involve the liver directly and probably more frequently cause hepatic jaundice Again hepatic involvement may actually result in post hepatic type jaundice by involvement of the larger hepatic ducts in the porta hepatica This is especially true of tertiary syphilis of the liver where the large scars may contract and compress the hepatic ducts This leads us into group IV or cicatricial stenosis of the bile ducts This group is clearly post hepatic in location and surgical in therapeutic approach

The various inflammatory lesions that can compress and occlude the bile ducts by edema and abscess formation may result in an extension of the process to the liver and hepatic jaundice The same can be said about the parasitic diseases but especially distomiasis (Chapter 34) Ascaris lumbricoides may penetrate into bile ducts and cause post hepatic jaundice but may also penetrate into liver forming a liver abscess and with this the possibility of hepatic jaundice arises

Post Hepatic Jaundice NOT Always Surgical

While in most instances of post hepatic jaundice surgical removal of the mechanical obstruction or short circuiting operation is the treatment of choice in some of the conditions listed above other forms of therapy may be preferable Hence post hepatic (obstructive) jaundice and surgical jaundice are not always synonymous After one has decided that a given case of jaundice is due to an obstruction of the common duct the type of obstruction should be ascertained (if possible) before surgery is resorted to Examples of this lack of identity between the two may be found in groups listed except group I (*calculi*) When the neoplasms involve the hepatic ducts in the porta hepatica surgery would be of no avail A more important example is lymph node involvement with Hodgkin s granuloma lymphosarcoma or leukemia These lymph nodes may respond to radiation or chemotherapeutic agents and surgery may become unnecessary This is also true of tuberculosis and syphilis of lymph nodes since *these granulomatous lesions can be effectively* treated by means of the newer antibiotics and chemotherapeutic agents

Inflammatory lesions of a nonspecific nature causing bile duct obstruction as well as hel

minthic obstruction of bile ducts may likewise be responsive to therapeutic agents other than surgery Therefore while we must conclude that not all types of post hepatic jaundice are surgical the majority of cases of post hepatic jaundice are surgical

Clinical and Laboratory Features of Post Hepatic Jaundice

General features of entire group are shown in Table 16 p 86

Symptoms

Since the commonest cause of post hepatic jaundice is cholelithiasis (Table 19) the patient may give a history of previous attacks of biliary colic and long standing dyspepsia due to ingestion of fatty foods Indeed the pain may be the severe episodic pain characteristic of this entity or the dull aching pain extending to the lumbar region seen in carcinoma of the pancreas (vide infra) The jaundice is fluctuating in benign lesions or constantly increasing in malignant lesions Pruritus is a frequent accompaniment of jaundice Acholic stools are either constant or intermittent as in the fluctuating jaundice Chill and fever are a frequent feature of common bile duct obstruction due to stone (Charcot s intermittent fever)

TABLE 19

Causes of Various Types of Jaundice

	Number		Per cent	
Intrahepatic jaundice				
Hepatitis	60	175		4 5
Cirrhosis	91			
Dystrophy	4			
Extrahepatic jaundice				
Calculus	15	37	36 9	57 5
Carcinoma of pancreas	63		15 3	
Biliary carcinoma	15		3 6	
Stricture	7		1 7	

The designation biliary carcinoma refers to malignant lesions other than neoplasms of the pancreas such as carcinoma of the gallbladder carcinoma of the bile ducts and metastatic carcinoma

From Lipp Lerner and Aaron J A M A 137 36 1948

Physical Findings

Jaundice is quite intense and depends on duration of obstruction and whether it is continuous or intermittent The skin has a greenish cast unlike the color in the other types of jaundice This is especially true in malignant obstruction This fine variation in color is sometimes deceptive since in intense hepatic jaundice the greenish tint may also develop The gallbladder may be palpable and tender *A palpable gallbladder is absolute evidence of post hepatic jaundice* This finding should therefore be looked for assiduously Tenderness confined to the gallbladder area and not over the entire liver is a helpful distinguishing feature from hepatitis Fist percussion tenderness is absent in post hepatic jaundice Liver enlargement is present in this group as well as in the other but gross nodularity of this organ as well as a palpable mass not attached to the liver suggest a neoplasm and probably post hepatic jaundice The spleen is usually not palpable in this type of jaundice

Laboratory Features

The blood count usually shows a normal erythrocyte count and hemoglobin or these may be slightly decreased The exception to this is when gross hemorrhage has occurred in malignant obstruction or more rarely now owing to hypoprothrombinemia Marked leukocytosis may be an important distinguishing feature between post hepatic obstruction due to a calculus and intrahepatic obstruction due to hepatitis Along with the leukocytosis there is an increase in the neutrophil

The pigment findings in blood and excreta are characteristic in the phases of complete obstruction (Table 15) The urine contains bilirubin but no urobilinogen the stools are acholic (negative for urobilinogen) and the bilirubin in the blood is high in the prompt reacting type The ratio between the prompt and delayed reacting bilirubin depend on the degree of icterus (Table 4) The pigment excretion becomes confusing when the obstruction is intermittent When the obstruction releases urobilinogen appears in the stool and

there may be temporary increase of urinary urobilinogen In this stage confusion with intrahepatic biliary obstruction is readily made Urinary urobilinogen likewise increases immediately after obstruction while urobilinogen is still being absorbed from the intestine

Stools may also contain occult blood which suggests a malignant obstruction however this finding is not too reliable in distinguishing post hepatic from hepatic jaundice since occult blood in the stool may be detected in the stools in hepatitis for poorly understood reasons

The tests attributable to parenchymal cell damage are characteristically normal in post hepatic jaundice This however holds true for the early stages of obstruction since prolonged obstruction eventually produces hepatocellular damage by virtue of back pressure of bile (cholestatic hepatitis) or ascending infection (cholangitic hepatitis) The reactions to these tests should therefore be evaluated in their proper perspective if positive Among these tests are to be included the serum albumin and globulin the flocculation and serum cholinesterase tests

The gamma globulin may show an early rise especially if there is an inflammatory process going on such as cholangitis In spite of a rising serum globulin the flocculation tests have a tendency to remain negative As a matter of fact the thymol turbidity may be lower than in normal individuals The serum of patients with post hepatic jaundice seems to have an unknown factor which inhibits the flocculating effect of gamma globulin Nevertheless in long standing post hepatic obstruction I have seen the result of the cephalin cholesterol flocculation test become 2 or 3 plus

The per cent of cholesterol esters as has been pointed out before may show a drop early in post hepatic jaundice but this is frequently accompanied by a high total cholesterol level (see p 34) The absolute value of cholesterol esters usually *remains normal* Because of an occasional early drop in cholesterol esters in post hepatic as well as hepatic icterus this test is not very useful in the differential diagnosis of jaundice however a high total cholesterol value with only a slight or no drop in the absolute value of cholesterol esters is suggestive of post hepatic jaundice (Table 17) Hepatic jaundice caused by the group of diseases classified as biliary cirrhosis likewise may show cholesterol and cholesterol ester values seen in post hepatic jaundice (Chapter 59) In post hepatic as well as hepatic jaundice the serum phospholipids vary in a parallel fashion with the total cholesterol (Albrink and collaborators)

A high alkaline phosphatase level is one of the important diagnostic features of post hepatic jaundice A markedly elevated alkaline phosphatase level and normal hepatocellular tests (especially the flocculation tests) are considered diagnostic of post hepatic jaundice The alkaline phosphatase elevation must be marked and parallel the serum bilirubin Thus this enzyme is usually found in concentration of 10 Bodansky units or higher in post hepatic jaundice The elevation if any in hepatic jaundice is usually below 10 units One must be sure what method is used for the alkaline phosphatase determination since the normal values vary widely In general in post hepatic jaundice the alkaline phosphatase elevation keeps pace with the serum bilirubin elevation while in hepatic jaundice this parallelism is not evident (p 90) A high alkaline phosphatase level is characteristic of biliary cirrhosis and may occur in other hepatic types of jaundice it cannot be used categorically as evidence of post hepatic jaundice (p 449)

The plasma vitamin A level has been suggested as a differential test between hepatic jaundice (hepatitis) and post hepatic jaundice (common duct obstruction) White and associates found the mean vitamin A level below normal (normal 30 micrograms) in hepatitis (20 6 micrograms) but normal or above (45 2 micrograms) in post hepatic obstruction Serum iron values were found low in post hepatic jaundice by Ducci and Spoerer They therefore consider a value *of over 300 micrograms* per 100 cc as evidence against post hepatic jaundice however they found low iron values in cirrhosis but high values in hepatitis High serum iron values were found by Metassarin and Delp in cases of hepatocellular injury

In most instances an intelligent analysis of the clinical and laboratory features of a given case should result in differentiation among prehepatic hepatic and post hepatic jaundice The most difficult diagnostic problems lie in differentiating between the last two In these two groups the greatest difficulty arises in distinguishing (1) hepatocanalicular (intrahepatic biliary obstruction) especially when complete (2) incomplete or intermittent post hepatic jaundice and (3) prolonged post hepatic jaundice with secondary hepatocellular involvement Any of these three types of jaundice may show features foreign to its therapeutic group Thus the first group may appear to be a surgical jaundice and the last two and especially the last may easily masquerade as medical jaundice Needle biopsy of the liver may be crucial in a differentiation (p 90 Table 18) however sometimes this procedure may also fail to supply conclusive evidence With the use of a composite approach the incidence of error in diagnosis becomes very low In the series reviewed by Lipp and associates in which this combined approach was used an error in diagnosis was made in only 2 4% In the occasional case where this differentiation cannot be made clinically one must weigh the benefits and dangers of surgical exploration Even surgical exploration may be deceptive I have seen a small neoplasm obstructing the hepatic duct missed at surgical exploration Properly done cholangiograms during surgery should eliminate such errors (Fig 16)

Patients with parenchymatous liver disease

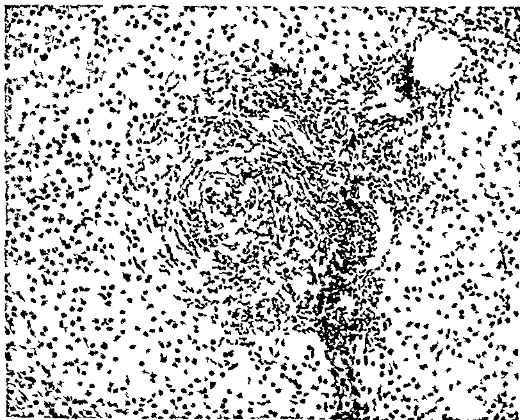


Fig 16 Liver needle biopsy (X 100) showing intense lymphocytic infiltration in periportal and intralobular ... with some periportal hepatic cell degeneration This is compatible with viral hepatitis Clinical picture was suggestive of choledocholithiasis Surgery was withheld because of biopsy result Subsequent course confirmed the histologic diagnosis

respond poorly to surgery and no one in this country recommends exploration and irrigation of extrahepatic bile ducts in hepatitis although the Scandinavian literature does contain reference to the beneficial effect of mechanical removal of inspissated mucus and bile from the biliary passages A rapid downhill course after surgical meddling in hepatitis has been observed however the patients who show no evidence of parenchymal damage but only evidence of biliary obstruction may be safely carried through a surgical procedure especially when this is done under local anesthesia A cholangiogram may be done with a minimum of manipulation and may reveal extrahepatic obstruction In any event when the preponderance of evidence points to an extrahepatic obstruction and the jaundice persists the danger of permanent damage from an unrelieved benign obstruction of the common duct may be greater than the risk of surgical exploration in an occasional case of hepatitis This problem is discussed in a recent paper by Stein and associates

16

Diseases of the Gallbladder and Extrahepatic Biliary Ducts

Anatomy of Gallbladder and Extrahepatic Bile Ducts

It will be profitable to review briefly the anatomy and function of the gallbladder and biliary ducts as they relate to the problem of post hepatic jaundice The liver normally secretes 500 to 700 cc of bile per 24 hours The bile drains out of the liver through the right and left hepatic ducts which leave the corresponding lobes of the liver Another duct from the caudate lobe joins the left hepatic duct The right and left hepatic ducts join to form the common hepatic duct which is about 4 cm long and 4 mm in diameter It joins with the cystic duct to form the common bile duct or ductus choledochus

The common bile duct is 7 5 cm in length and about 6 mm in diameter It descends toward the second portion of duodenum its terminal portion is in close apposition to and occasionally embedded in the head of the pancreas along the terminal portion of the pancreatic duct The two ducts join to form a slightly dilated common passage the ampulla of Vater which opens into the medial side of the second portion of the duodenum through the duodenal papilla This is located about 10 cm from the pylorus

The intramural portion of the ductus choledochus is encircled by muscle fibers the *sphincter choledochus* In about one third of subjects there is a sphincter at the terminal end of the pancreatic duct and a third sphincter encircles the ampulla These three sphincters collectively are known as the *sphincter of Oddi* This sphincter as well as the gallbladder are important in regulating the entrance of bile into the gastrointestinal tract

The *secretory pressure* of the liver is about 30 cm of water The resistance of the sphincter of Oddi varies between 9 and 25 cm of water but may at times be as high as 75 cm The secretion of bile by the liver is continuous and in the interdigestive period the resistance of the sphincter is higher than the secretory pressure

of the liver resulting in a drawing back of bile into the gallbladder

The gallbladder is normally about 7 to 10 cm long and 2 5 cm in its greatest diameter and has a capacity of about 35 cc It empties into the common bile duct through the cystic duct which is 3 5 cm long and 3 mm wide The final portion of the duct has 5 to 7 crescentic folds of the mucosa giving the appearance of a spiral valve (Heister s valve valvula spiralis) The bile entering the gallbladder is concentrated ten or twenty fold so that the entire 24 hour bile secreted by the liver can be stored in the gallbladder When the gallbladder receives the bile its musculature is relaxed The expulsive power of the gallbladder is equal to 20 to 30 cm of water This is insufficient to force concentrated gallbladder bile into the liver but is sufficient to force bile into the duodenum during relaxation of the sphincter of Oddi

The concentrating and storage properties of the normal gallbladder delay the onset of jaundice Ligation of the common duct in a dog with an intact gallbladder results in jaundice in 36 to 48 hours while if the cystic duct is ligated or the gallbladder removed first jaundice results in six hours or less

Post hepatic jaundice may result from a blockage at various levels of the extrahepatic biliary ducts (1) the two branches of the hepatic duct (2) the common hepatic duct (3) the common bile duct or (4) the ampulla of Vater Obstruction of the cystic duct in itself should not cause icterus but secondary edema of the common duct frequently occurs with resultant post hepatic jaundice Motor derangements of the sphincter of Oddi may result in transient obstruction at this level with transient jaundice

Biliary Dyskinesia (Biliary Dyssynergia)

Biliary dyskinesia is a clinical syndrome resulting from a neuromuscular disturbance of the mechanism controlling the emptying of the gallbladder and ejection of bile from the gallbladder and biliary tree into the duodenum The most important factors that are responsible for this disturbance consist of alteration in pressure relationships between the sphincter of Oddi intraductal pressure (choledochus) and pressure developed by the contracting gallbladder The two main types of biliary dyskinesia are (1) *the primary type* occurring in individuals with an intact gallbladder and biliary ducts and (2) *the secondary type* occurring in cholecystectomized patients (post cholecystectomy biliary dyskinesia)

Primary Biliary Dyskinesia

The first type of biliary dyskinesia is rare and relatively unimportant from the point of view of production of jaundice However mild transient icterus has been described accompanied by attacks of pain simulating biliary colic The mechanism is presumably a spasm of the sphincter of Oddi creating a resistance of above 30 mm water which the contracting gallbladder with a pressure under 30 mm is unable to overcome The contraction of the gallbladder against the higher resistance produces pain and if the spasm continues long enough bile regurgitates into the liver and eventually into the blood resulting in jaundice

This syndrome has to be differentiated from cholelithiasis Usually a cholecystogram will show normal filling and concentration of dye in the gallbladder and an absence of shadows indicative of calculi Sluggish emptying of the gallbladder and the development of pain with a fatty meal is confirmatory evidence

Royer and co-workers studied biliary dyskinesia by means of peritoneoscopic cholangiography The radiopaque material was injected slowly into the gallbladder under peritoneoscopic control Normally the hepatic ducts do not fill (this may be due to sphincteric action of the hepatic duct [Mirizzi]) and the common duct is less than 8 mm in diameter In biliary dyskinesia the hepatic and intrahepatic ducts fill because of the higher resistance of the sphincter of Oddi If the common duct is dilated above 8 mm they postulate an organic obstruction of the choledochus (Others regard dilatation of the common duct in biliary dyskinesia as a possibility)

Secondary Biliary Dyskinesia

Secondary or postcholecystectomy biliary dyskinesia is commoner than the primary type

respond poorly to surgery and no one in this country recommends exploration and irrigation of extrahepatic bile ducts in hepatitis, although the Scandinavian literature does contain reference to the beneficial effect of mechanical removal of inspissated mucus and bile from the biliary passages A rapid downhill course after surgical meddling in hepatitis has been observed however the patients who show no evidence of parenchymal damage but only evidence of biliary obstruction may be safely carried through a surgical procedure especially when this is done under local anesthesia A cholangiogram may be done with a minimum of manipulation and may reveal extrahepatic obstruction In any event when the preponderance of evidence points to an extrahepatic obstruction and the jaundice persists the danger of permanent damage from an unrelieved benign obstruction of the common duct may be greater than the risk of surgical exploration in an occasional case of hepatitis This problem is discussed in a recent paper by Stein and associates

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The first type of biliary dyskinesia is rare and relatively unimportant from the point of view of production of jaundice However mild transient icterus has been described accompanied by attacks of pain simulating biliary colic The mechanism is presumably a spasm of the sphincter of Oddi creating a resistance of above 30 mm water which the contracting gallbladder with a pressure under 30 mm is unable to overcome The contraction of the gallbladder against the higher resistance produces pain and if the spasm continues long enough bile regurgitates into the liver and eventually into the blood resulting in jaundice

This syndrome has to be differentiated from cholelithiasis Usually a cholecystogram will show normal filling and concentration of dye in the gallbladder and an absence of shadows indicative of calculi Sluggish emptying of the gallbladder and the development of pain with a fatty meal is confirmatory evidence

Royer and co-workers studied biliary dyskinesia by means of peritoneoscopic cholangiography The radiopaque material was injected slowly into the gallbladder under peritoneoscopic control Normally the hepatic ducts do not fill (this may be due to sphincteric action of the hepatic duct [Mirizzi]) and the common duct is less than 8 mm in diameter In biliary dyskinesia the hepatic and intrahepatic ducts fill because of the higher resistance of the sphincter of Oddi If the common duct is dilated above 8 mm they postulate an organic obstruction of the choledochus (Others regard dilatation of the common duct in biliary dyskinesia as a possibility)

Secondary Biliary Dyskinesia

Secondary or postcholecystectomy biliary dyskinesia is commoner than the primary type

Residual symptoms following cholecystectomy occur in 10 to 40% of patients after this operation The lower figure applies to patients with calculous gallbladders while the higher figure applies to those with noncalculous gallbladders There are several factors responsible for these residual symptoms In patients with cholelithiasis a missed common duct stone or even a calculus in the stump of the cystic duct must be considered In some of these individuals no organic cause for the pain and the jaundice is to be found The pain may simulate biliary colic and be accompanied by chills fever and jaundice The jaundice is usually not deep is transient and is caused by incomplete obstruction The chills and fever are rare and are expressions of cholangitis

The pathogenesis of the postcholecystectomy *biliary dyskinesia is as follows When the gall* bladder is removed the pivotal factor for maintaining a balanced pressure relationship in the extrahepatic biliary tree is eliminated The *sphincter of Oddi which normally relaxes in* response to contraction of the gallbladder remains in a state of increased tonus in the absence of this stimulus for relaxation The increased tonus of the sphincter of Oddi is a frequent occurrence after cholecystectomy but is usually of short duration It may be responsible for the increased jaundice or the development of jaundice for 24 or 48 hours postoperatively In the majority of instances the sphincter eventually relaxes or relaxes in response to the secretory pressure of the liver The increased tonus of the sphincter of Oddi may result in a dilatation of the common duct and the contraction of the common duct may supply the stimulus lost with cholecystectomy

In some cases this favorable evolution does not take place and the sphincter of Oddi remains in a state of intermittent spasm with most of the symptoms of choledocholithiasis Colp has reported eight instructive cases of this type in which surgical exploration showed no other cause for obstruction except a hypertrophied and spastic sphincter of Oddi The response to sphincterotomy in these cases was gratifying Some of these patients showed dilated common ducts

Hicken and co workers on the basis of their studies of 1700 cholangiograms in cholecystectomized patients disagree with many of the current conceptions referred to They found no instance of compensatory dilatation of the common duct after cholecystectomy nor evidence of disturbed tonus of the sphincter of Oddi When a dilated duct was found some organic cause was found to account for it These authors also deny that increased intraductal pressure is responsible for pain in cholecystopathies since over 400 mm of water pressure was required to elicit pain They think that inflammatory and chemical irritation of the duct lowers the pressure threshold for pain so that pain occurs with lower pressures It is also a well known fact that the rapidity with which the pressure is increased *influences the pain threshold*

Dreiling suggested a *secretin test* to determine the presence of a partial obstruction of the common duct after cholecystectomy In a *normal individual with an intact gallbladder* there is a decrease of bile in the duodenal drainage in response to secretin and the icteric index of the duodenal contents falls The increased bile secreted by *the liver is stored* in the gallbladder while the sphincter choledochus remains closed When the gallbladder is nonfunctioning or has been removed the bile drains into the duodenum and the icteric index of the duodenal contents remains high If the response in a cholecystectomized patient is similar to the response seen in a normal individual it is indicative of retention of bile in the bile ducts and a partial obstruction of the common bile duct This test does not differentiate among an obstruction due to a calculus a cicatrix or spasm of the sphincter Although Dreiling found that the cause of obstruction in most of his cases was spasm surgery may be necessary to rule out cicatricial or calculous obstruction The presence of cholesterol and calcium bilirubinate crystals in the sediment would suggest that calculi are present

While it should be emphasized that dyssynergias of the gallbladder and extrahepatic biliary ducts are not frequent causes of biliary

colic or jaundice it must be kept in mind that such cases may be occasionally encountered especially after cholecystectomy

ORGANIC DISEASES OF THE GALLBLADDER

General Considerations

Diseases of the gallbladder are the commonest causes of post hepatic jaundice Neoplasms of the gallbladder are rare and therefore relatively unimportant as compared with calculi and inflammations cholelithiasis and cholecystitis In cholelithiasis we are apt to think in terms of a mechanical obstruction and in cholecystitis in terms of inflammation Actually the two processes are interwoven and interdependent Thus in acute cholecystitis calculi are present in 93% of cases while bacterial invasion of the gallbladder occurs regularly after obstruction of the common or cystic duct

Role of Infection

Cholelithiasis and obstruction precedes bacterial inflammation and the obstructive phenomenon is apparently necessary for acute inflammation In the first 24 hours after development of the clinical picture of acute cholecystitis 65% of gallbladders are sterile The incidence of positive cultures increases to 80% after the third day of illness (Goldman and associates Andrews and Henry)

Role of Mechanical Chemical and Circulatory Factors

Mechanical chemical and circulatory factors are all important in the initiation of acute cholecystitis Even in empyema and gangrene of the gallbladder cultures may remain sterile With obstruction of the outlet from the gallbladder the bile becomes highly concentrated and the changed chemical composition may be injurious to the gallbladder wall This may be coupled with increased intraluminal pressure and vascular compression

The Rokitansky Aschoff sinuses may play a special role here These sinuses have been described as branching evaginations of the mucous membrane of the gallbladder extending in finger like fashion into the muscularis Increased intraluminal pressure can result in a marked distention of these sinuses with concentrated bile The distal end of these sinuses may dilate and be pinched by contraction of the surrounding muscle fibers This increased pressure and dilatation of these sinuses may compress the vascular supply and result in gangrene

Pathogenesis of Biliary Calculi

Important contributing factors in the pathogenesis of biliary calculi are (1) bile stasis and (2) changes in composition of bile The increased bilirubin excretion in hemolytic disease with the formation of bilirubin stones is an example of the second factor Cholesterol stone formation may depend in part on increased cholesterol excretion or reduction of bile salts which help to keep the cholesterol in suspension In regard to the latter I have seen the development of biliary calculi in several young male patients after an attack of homologous serum hepatitis Because of the rarity of cholelithiasis in young males the possibility of the abnormal composition of the bile during the hepatitis is an attractive theory of its genesis Infection while of minor importance may by forming a nidus of bacteria and desquamated epithelium result in the development of a calculus

Influence on the Liver

Diseases of the gallbladder are important not only because of their relationship to post hepatic jaundice but also because of their influence on the liver The liver is influenced by the two mechanisms that play a role in the propagation of cholelithiasis and cholecystitis (1) obstruction with back pressure on the liver and (2) infection spreading to the liver via the bile ducts (see page 115)

ACUTE CHOLECYSTITIS

Clinical Features

Acute cholecystitis like cholelithiasis is most commonly seen in middle aged obese women although it is occasionally seen in the older age group and even in children The ratio of

females to males is as high as 4 to 1 Negroes except those suffering from sickle cell anemia much less commonly succumb to gallbladder disease A history of previous attacks of similar but milder degree may be elicited in four fifths of patients

Symptoms

Pain is an outstanding feature and is of the type usually referred to as biliary colic It frequently begins late at night or in the early morning hours several hours after a heavy meal The pain is not always colicky in spite of its name but on the contrary may be steady sharp and mounting in severity While the right upper abdominal quadrant with extension to the right subscapular area is the classical region of the pain it may be epigastric or subxiphoid and extend to the left side downward or the tip of the right shoulder A typical location or radiation of pain may complicate the diagnosis since it can be confused with pancreatitis cardiospasm perforating ulcer and appendicitis

Nausea and vomiting are frequent occurrences although they may be absent If vomiting occurs it may recur many times and is said to indicate stone outside of the gallbladder in the cystic or common duct

Chills and chilly sensations especially the latter are frequently present at the onset Frank shaking chills are more commonly present in choledocholithiasis

Physical Findings

Jaundice occurs in only about 25% of cases The jaundice is not due to obstruction of the common duct by a calculus but rather to a compression of the common duct by an edematous cystic duct and enlarged and inflamed gallbladder or to edema and extension of inflammation to the common duct The jaundice is therefore not likely to be severe, prolonged or continuous

Fever is usually low grade (one or two degrees Fahrenheit above normal) but if the disease progresses to empyema or gangrene the temperature may be as high as 103 or 104 F

Tenderness is usually quite marked over the anatomical location of the gallbladder This is almost always elicited during the acute attack of pain and the tenderness is accompanied by muscle guarding The localization of the tenderness over the gallbladder area rather than the entire liver helps in distinguishing acute cholecystitis from acute hepatitis

A mass is occasionally palpable in the gallbladder region consisting of the gallbladder omentum and adjacent bowel The gallbladder may be palpable in hydrops of the gallbladder

Tympanitis may occasionally be found because of a low grade secondary ileus in which case the bowel sounds are reduced in frequency or absent With gangrene or perforation of the gallbladder the abdomen becomes silent tympanitis increases and generalized spasm of the abdominal muscles takes place

Laboratory Features

Leukocytosis when present is very useful in differentiating this condition from other causes of jaundice such as hepatitis However in about half the cases the white count is at the upper limits of normal or about 10 000 A leukocyte count of over 15 000 does occur in about 20% of patients

Elevated serum bilirubin is found in a slightly larger number of patients than is clinical icterus The hyperbilirubinemia is mild and consists chiefly of the immediate reacting type The alkaline phosphatase is elevated in patients with jaundice but may be slightly elevated in those with normal serum bilirubin

The urine shows bilirubin and a normal or slightly increased amount of urobilinogen This slight hyperbilirubinuria is due to a combination of incomplete obstruction of the common bile duct plus slight impairment of the liver

Liver function tests may show slight deviation from normal this will depend largely on the severity and duration of the infection and obstruction This entire problem will be discussed in greater detail later Suffice it to say that the abnormal liver function tests when they occur make the differential diagnosis more difficult and add a hepatic factor to the post hepatic factor in the production of jaundice

Summary

Female 4 1
Middle age—past 40
Negroes uncommon (except in those with
 Sickle cell disease)
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 Mass
 Tympanitis
Laboratory
 Leukocytosis in 50% of cases—over 15 000 in 20% of cases
 Hyperbilirubinemia—prompt reacting
 Alkaline phosphatase elevated
 Urobilirubinuria

Chronic Cholecystitis

Chronic cholecystitis in a noncalculous gallbladder is probably very rare if strict criteria are used for its diagnosis Histologic evidence of chronic inflammation has been demonstrated in the absence of calculi however the passage of a stone into the intestine cannot always be excluded When chronic cholecystitis develops in the absence of calculi some other type of mechanical obstruction of the cystic duct may be responsible for the process Noncalculous chronic cholecystitis is of little importance in the differential diagnosis of jaundice since jaundice is a rare concomitant of this condition Chronic calculous cholecystitis is discussed under cholelithiasis

Cholelithiasis

Clinical Features

The clinical features of cholelithiasis are similar in many respects to acute cholecystitis The reason for this is easy to see The diagnostic symptoms and the ones that usually cause a patient to seek medical care are due to obstruction of the cystic duct with a calculus This is precisely the factor involved in most of the cases of acute cholecystitis The development of fever chills and marked tenderness results in classification of the attack as acute cholecystitis Indeed in chronic cholelithiasis when biliary colic occurs mild acute cholecystitis is probably present The inflammatory feature may remain subclinical and the mechanical factors are perceived by the physician and the patients

The various types of dyspepsias which have been attributed to chronic cholecystitis and cholelithiasis have not been proved to be due to gallbladder disease Thus the selective dyspepsia due to fat ingestion nausea belching and postprandial distress between attacks of colic occur only in a small percentage of patients Occasionally I have seen a patient with atypical dyspepsia and no colic who experienced complete relief from the removal of a calculous gallbladder Asymptomatic cholelithiasis is not too common if a painstaking history is obtained Mild attacks of pain not of the magnitude to deserve the term biliary colic and disregarded by the patient are experienced by those not having the violent attacks of pain

The age sex and race distribution is the same as for acute cholecystitis Windley however found cholelithiasis three times commoner in the Negro than in the white hospital population at the New Orleans Charity Hospital Garrish and Cole found two cases of cholelithiasis in 41 cases of surgical jaundice in children under 12 years of age One of these had congenital hemolytic icterus and the other inflammatory stricture of bile ducts Hemolytic

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- **Chills and chilly sensations**

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- **Tenderness over gallbladder area**
- **Muscle guarding**
- **Mass**
- **Tympanitis**

Laboratory
- **Leukocytosis in 50% of cases—over 15 000 in 20% of cases**
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the duodenum One having a metal weight at the terminal end (Rehfuss tube) is passed more easily through the pylorus Indeed this is the most difficult and time consuming part of the procedure If the patient lies on his right side and takes a few sips of water the passage of the tip of the tube through the pylorus is facilitated Aspiration of clear golden yellow bile is an indication of proper positioning of tube and may not require fluoroscopic confirmation The duodenum is about 75 cm from the incisor teeth as measured by the tube Therefore it there is a 75 cm mark on the tube this may be used as a gauge for the proper passage of the tube

In order to stimulate the emptying of the gallbladder 75 cc of 33% solution of magnesium sulfate is introduced into the duodenum by gravity This can be allowed to drain out after a few minutes and more magnesium sulfate introduced later The original publications of Lyon may be consulted for a detailed description of this procedure Bockus also gives an elaborate description of the technique

Types of Bile

The bile obtained by this procedure is ordinarily divided into three types *A bile* is the first portion of golden yellow bile obtained and presumably comes from the common bile duct *B bile* is dark brown bile which consists of the concentrated bile of the gallbladder and *C bile* is the golden yellow bile that follows the second portion of bile and is considered to come from the hepatic duct

Examination of the Bile

The gross appearance of the bile is of some diagnostic significance Thus excessively dark concentrated and viscid B bile is an indication of gallbladder stasis The absence of characteristic B bile suggests a defect in emptying of the gallbladder Another stimulant such as olive oil, may be tried If no B bile is obtained after further stimulation it may be due to an obstruction of the cystic duct If no bile of any kind is obtained complete obstruction is the explanation If the bile stained fluid is very pale and obviously contains little bilirubin it may be due to intrahepatic obstruction with parenchymal damage Partial extrahepatic obstruction should yield small amounts of dark, concentrated bile

Chemical Determinations

Such determinations of the various fractions of bile obtained will show the increased concentration of bilirubin and cholesterol in the B bile and the degree of concentration of these substances will be an index of the concentrating power of the gallbladder and the presence of stasis The concentration of bile acids and salts would yield further information as to the integrity of the hepatic cells but these complicated procedures are not ordinarily done

Microscopic Examination

This is a simple and yet a most important part of the procedure The examination of the sediment obtained on standing or after centrifugation should not be delayed for more than several hours because too long a delay may introduce artefacts The finding of cholesterol crystals and/or calcium bilirubinate is indicative of cholelithiasis for this reason microscopic examination is a useful procedure in a given case of jaundice that cannot be definitely classified as to etiology Bockus and co workers reported that 100% of their patients showing both of these in the sediment were found to have cholelithiasis at surgery Even if this perfect score is not always attainable the finding of both or either one of these substances in the sediment is a good indication of cholelithiasis

The cholesterol crystals are easy to identify They consist of thin rectangular transparent sheets with some irregularity in their geometric configuration The calcium bilirubinate is a golden yellow or deep orange granular precipitate found in masses and sometimes intermixed with the cholesterol crystals The finding of cholesterol crystals and calcium bilirubinate in only one of the fractions of bile may indicate not only the presence of stones but their location in the biliary tract as well

In addition to these chemical substances the organized sediment of cells and bacteria may be of diagnostic importance Columnar epithelial cells if found in large numbers may be

indicative of inflammation of the bile ducts or the gallbladder Numerous polymorphonuclear cells indicate cholecystitis or cholangitis or both With the recent interest in cytological studies for malignant lesions atypical neoplastic cells may give an indication of carcinoma of the gallbladder bile ducts or pancreas

Summary

Technique

1 **Rehfuss tube into second portion of duodenum**
2 **Aspirate golden yellow bile (A bile)**
3 **Insert by gravity 75 cc of 33% solution of $MgSO_4$ olive oil may be used as another cholagogue**
4 **Aspirate bile after $MgSO_4$ (B bile)**

Types of bile

1 **A bile—golden yellow from common bile duct**
2 **B bile—concentrated dark brown bile from the gallbladder**
3 **C bile—golden yellow bile from hepatic ducts**

Examination of bile

Gross appearance

Dark concentrated viscid B bile suggests biliary stasis

Absence of B bile suggests defective emptying of gallbladder obstruction of cystic duct

No bile obtained indicates obstruction of common duct

If bile is very pale intrahepatic biliary obstruction is suggested

Small amounts of dark concentrated bile indicate partial post hepatic obstruction

Chemical determinations

Yield information concerning concentration of pigment and bile acids

Microscopic examination

Sediment obtained by standing or centrifugation

Avoid long delay

Findings

Crystals of

a **cholesterol and or**
b **calcium bilirubinate are diagnostic of cholelithiasis**

Cells

Bacteria in great numbers indicate infection

Columnar epithelium indicates bile duct inflammation

Polymorphonuclear cells indicate inflammation

Neoplastic cells

Examination of the feces after an attack of biliary colic may occasionally reveal the presence of a calculus Small calculi are known to pass through the cystic and common duct and down through the intestines

Other tests including blood count liver function tests and urinalysis show alterations similar to those seen in acute cholecystitis if they are done during the biliary colic The leukocyte count is not likely to be elevated If jaundice is present the findings are usually those of post hepatic icterus The effect of the various types of gallbladder disease on the liver and liver function tests will be discussed later

Choledocholithiasis

Clinical Features

Obstruction of the common duct with biliary calculi is by far the most important cause of post hepatic jaundice to be considered in the differential diagnosis Its importance lies (1) in its frequency (2) in the frequency with which it produces jaundice and (3) in its responsiveness to surgical intervention

Choledocholithiasis occurs in 13 to 20% of patients with cholelithiasis While no age group is immune it is most frequent in the fifth and sixth decade Females are at least twice as prone to it as males With advancing years this discrepancy is less marked while in the young adults it is greater In infants it is equally rare in both sexes however to avoid catastrophic diagnostic errors it must be remembered that it does occur before puberty (Ulin and coworkers)

Symptoms The classical sequence of symptoms if present makes the diagnosis simple These are (1) biliary colic ( ) jaundice and (3) chills and fever All three unfortunately are not always present

Pain is similar to that described under

TAB E O

Compa on of 75 Ca es of Common Duct S one w h 49 Cases of Carc noma of he Head of the Pancreas (Con e u e Ca es

Symp m F nd t	*D g*	
	C mm d er	*C f h h d f p er*
Past h ory sugge ve of gal blad de d ease	100	18
Col c	9	16
Locat on of pa n		
R ght uppe quad ant	53	0
Ep ga m	40	33
Lef uppe quad an		2
Ref red to ba k	67	18
We gh lo s	25	86
Jaund e		
Inc den	8	86
In e m en	35	
Vom ng	77	7
Ch l	3	8
Sex		
Mal	3	69
Femal	87	3
En a ged ga lbladd		55
Enlarg d l e	25	80
Ope a e mo a	10	3
Age n e a er ge	5	58

F om Zo nge and Kevo k an

cholel th as It may be ep gastr c n tl e r ght upper abdom nal quadrant or even n the left upper quadrant b t tl e last unco nmon Extens on to the left subscapular area s most character st c but the pa n may extend toward the left s de and even to the lumbar reg on vh cl confu es tl e d agnos s The severe pa n des gnated as col c may be ab ent n as h gh as o or 25% of cases (Berk and otl ers) In 2 to 6% of cases pa n may be absent completely (Jordan and We r) In Zoll nger and Kevor k an s ser es of 75 ca es 91% gave a h story of b l ary col c and 100% gave a h story suggest ve of b l ary tract d sease One m ght therefore say that typ cal col c may be absent so ne pa n s p esent n the vast major ty of pat ents and a l story of b l ary tract d sease s nearly al ways present (Table 20)

Dyspeps a wh ch ncludes belch ng bloat ng and fulness s very common Vom t ng s repeated and n ore pers stent than n cholel th as s Indeed repeated vom t ng s nd cat e of a calculus outs de the gallbladder

Jaund ce is present in 75 to 80% of cases The jaund ce may be m ld and trans ent even when deep t has a tendency to fluctuate becau e of tl e ntermittent character of the obstruct on Pruritus accompanies the jaund ce and may be most d stress ng

Ch lls and fever so called Cha cot s n er m ttent fever the last of the d agnost c tr ad is present in only about one th rd of pat ents (Table 20) Tl e temperature may be h gh up to 104°F w th an afternoon peak It s a s gn of cholang t s but not necessar ly of the sup purat ve type

Physical Fi dings

There are no d agnost c phys cal find ngs n th s cond t on A r ght upper abdom nal sca may be found from prev ous b l ary t act surgery Even a cholecystectomy does not n l tate aga nst a d agno s of choledochol th as s A cl olecystecto ny n a jaund ced pat ent may be follo ved by obstruct on of the common duct by an overlooked calculus

Tenderness over the gallbladder area ma be el c ted A palpable gallbladder may be present contrary to Courvo s er s la v and has been found in 12% of cases (Zoll nger and Ke o kian) The liver may be enlarged but is not markedly tender The spleen nay be palpable f repeated attacks of b l ary obstruct on ha e resulted n b l ary c rrhos s

Labora ory Feat res

Blood Leukocyto s s a he pful d agno c find ng but unfortunately t s pronounced only n those (about 33%) having cholangit s The other two th rds have moderate leukocytos s (10 000 to 12 000) If the e s no leuko cytos s n tl e pre ence of h gh fever and jaund ce it is good ev dence aga n t chole dochol th as s

B le pig nents and l ver f nct on Hype b l rub nem a s not marked and fluctua es achol c stools are nterm ttently present Uro b l nogenur a is absent dur ng the per od of complete obstruction and may be increa ed at the beg nn ng of the obstr ct on The alkal ne pl o phatase s markedly ele ated The total

cholesterol may be elevated but the cholesterol esters may be relatively decreased especially after prolonged obstruction There may be considerable disturbance of liver function which will be discussed later

Biliary drainage This is a very valuable diagnostic procedure and should be utilized more frequently in the differential diagnosis of jaundice Its chief drawbacks are that it may be a time consuming procedure if the tube does not pass readily through the pylorus and if an infectious hepatitis is present the disturbance to the patient may have a deleterious effect

X *ray* Cholecystography in the presence of jaundice and common duct stone would hardly be expected to yield useful results A flat plate of the abdomen may on occasion reveal radiopaque calculi in the region of the common duct

The following case illustrates an instance of lack of correlation between the clinical and laboratory findings and the confusion in diagnosis that would result from it

Case 2

O L male age 66 entered the hospital for plastic surgery following excision of a basal cell carcinoma of the face The intern noted that the patient was jaundiced *Pruritus* was present for two days and clay colored stools were noted by patient for ten days *Anorexia* was present for one week and a weight loss of 11 pounds occurred in the previous three weeks Frequency and nocturia were present for some time

The past history consisted of a peptic ulcer and hematemesis -5 years before for which surgery was done Recurrence of ulcer distress was noted 10 years and several months before this admission

Physical examination revealed the greenish type of jaundice a liver palpable at the umbilicus which was not tender to palpation but somewhat tender to percussion The spleen was not palpable

The clinical picture with pruritus and green jaundice developing without pain suggested



Fig 1 H d ps of g ll bladd r in a pat e t with c lcul u bstructi n of common d ct (ca e bove) Calcul s s sit ted r C

post hepatic jaundice The possibility of a malignant lesion causing it was strongly entertained and laboratory studies were made

Gastrointestinal x rays showed a well functioning gastroenterostomy and no evidence of neoplasm Stools were positive for occult blood Liver function tests were as follows Serum bilirubin 36 mg % alkaline phosphatase 15 Huggins units total protein 6 5 gm % total albumin 3 9 gm % and globulin 2 8 gm % cephalin cholesterol flocculation 4 plus thymol turbidity 7 4 u cholesterol total 90 mg and esters 41 mg Prothrombin time was normal

It will be noted that the results of liver function tests were in favor of hepatic rather than post hepatic jaundice The alkaline phosphatase was at the upper limits of normal in spite of very high serum bilirubin The flocculation tests and cholesterol both indicated hepatic dysfunction

This contradiction between the clinical and laboratory pictures resulted in delay of surgery The patient in the meantime took a precipitous downward course becoming lethargic the urea nitrogen rose to 130 mg and the creatinine to 5 2 mg with disturbance in electrolytes He died in coma 15 days after entering the hospital At autopsy a stone was found obstructing the common duct (Fig 17) The kidneys showed cholemic nephrosis (Fig 83) and the liver early biliary cirrhosis

Summary

Incidence 13 to 20% of patients with cholelithiasis
Age Fifth to sixth decade—occurs also in childhood
Sex Twice as common in females as in males
Symptoms
- **Pain—biliary colic similar to cholelithiasis severe colic may be absent in 20 to 25% pain may be totally absent in 2 to 6%**
- **Dyspepsia—precedes colic**
- **Vomiting is repeated and more persistent**
- **Jaundice in 75 to 80% of cases may be mild or deep but always fluctuating**
- **Pruritus**
- **Chills and fever in one third of patients**

Physical Findings
- **Right upper abdominal quadrant scar may be found—previous surgery**
- **Tenderness over gallbladder**
- **Palpable gallbladder in 12% of cases**
- **Spleen may be palpable after prolonged and repeated attacks**

Laboratory
- **Leukocytosis—pronounced in 33% of cases, 10 000 to 12 000 count in others**
- **Hyperbilirubinemia—moderate and usually fluctuates**
- **Alkaline phosphatase elevated above 10 B U**
- **Total cholesterol elevated—esters may become relatively depressed**
- **Liver function tests are normal early in first two weeks become disturbed later**
- **Biliary drainage may show absence of bile thick bile cholesterol calcium bilirubinate crystals pus cells**
- **Cholecystography—not helpful**
- **Flat x ray plate may yield radiopaque shadow**

Cholangiography

Indications

Cholangiography or the direct x ray visualization of the extrahepatic biliary ducts and gallbladder by injection of radiopaque substance is a most useful procedure under special circumstances Its field of usefulness is in jaundice after cholecystectomy, in suspected biliary dyskinesia in persistent jaundice having features of both extrahepatic and intrahepatic obstruction in cases of jaundice where surgical exploration is inconclusive or cannot be thoroughly performed It is recommended as a routine procedure in choledochostomy (Corff and co workers 1952) either by itself or with monometric determinations (Mallet Guy 1952)

Methods and Types

The types of cholangiographic procedure may be classified according to the mode of introduction of the radiopaque substance

1 *Immediate cholangiography* is the term applied to the introduction of the opaque substance and visualization of the ducts during surgical exploration

2 *Delayed cholangiography* is applied to the introduction of the opaque substance several days or longer after a surgical procedure through the surgically placed drainage tube

3 *Cholangiography* may be done by introducing the opaque substance through an external biliary fistula

4 *Peritoneoscopic cholangiography* is done by introducing the opaque substance into the biliary tree by peritoneoscopic guidance (Royer and collaborators) This is an ingenious procedure and may become a useful one

5 *Transabdominal cholangiography* is accomplished by injecting the opaque material blindly through the abdominal wall into one of the major hepatic ducts (Carter and Saypol) This seems to be a procedure fraught with great danger The patient in whom this was successfully accomplished from a technical point of view died several days later It is not clear whether the procedure was in any way responsible for the patient s death

Radiopaque Substances

The opaque substances that have been used for this purpose are Lipiodol Brompin or Bromminol Diodrast Umbrathor Thorotrast and Hippuran Lipiodol is a time honored radiopaque substance but by virtue of its oily nature is not miscible with the aqueous bile and may form globules and other artefacts that could be a source of error in interpretation The same objections may be raised against Bromminol which is a 33% mixture of bromine in sesame oil Hippuran (ortho iodo hippurate) is used as a 48% aqueous solution and is a satisfactory medium Diodrast (iodopyracet) 35% solution is readily available and satisfactory Umbrathor and Thorotrast containing the radioactive compound of thorium oxide have a possible disadvantage because of its radioactivity

The technique varies with the type of cholangiography done—immediate delayed peritoneoscopic etc If the test is done through a preexisting drainage tube or fistula the opaque substance is injected into these channels without preliminary preparation In the immediate and peritoneoscopic methods the dye can be injected into the common duct or gall bladder In either case 15 to 45 cc is aspirated before the opaque medium is injected slowly The medium used and the entire procedure is carried out with strict attention to asepsis

Usefulness

Postoperative Cholangiography is a most useful procedure in establishing or ruling out the presence of post hepatic obstruction in certain cases of jaundice In postcholecystectomy patients the development or increase of jaundice is most distressing to surgeon and internist alike It may be very difficult to decide whether the icterus is due to an overlooked common duct stone or an ascending cholangitis or hepatitis The presence of urobilinogen in the feces is compatible with an incomplete obstruction of the common bile duct and bile drainage from a T tube may be present in intrahepatic obstruction Filling of the extrahepatic bile ducts with an opaque medium may determine the point of obstruction The usefulness



Fig 18 Cholangiogram showing numerous faceted calculi filling the common duct The ducts were filled through the "T" tube in the common duct (Courtesy Dr L F Kirsh)

of cholangiography is emphasized by Hicken and associates on the basis of their experience with 750 cholangiograms

Biliary dyskinesia and hepatitis Its usefulness in biliary dyskinesia has already been alluded to If peritoneoscopic cholangiography were proved to be safe and feasible by wider use it would be of great help not only in this condition but in the differential diagnosis of obscure hepatitis from post hepatic obstruction Abdominal exploration occasionally has to be resorted to in order to eliminate the possibility of an extrahepatic obstruction in a patient with atypical hepatitis Peritoneoscopy would be preferable to surgical exploration of the abdomen Even if surgery is resorted to cholangiography may reduce the need for time consuming and traumatic exploration in a poor surgical risk

Interpretation

The following points are looked for in the interpretation of a cholangiogram

1 Filling of ducts Hepatic ducts do not fill normally and their filling may indicate dyskinesia (Royer and co workers)

2 Size of ducts Dilatation of the common duct is a sign of organic obstruction

3 Emptying of an opaque medium into the duodenum occurs readily if obstruction is present this does not take place

4 Oval radiopacities or radiolucencies in the common duct are indicative of calculi and are accompanied by abnormal responses in 2 and 3



Fig 19 Cholangiogram made by injecting 70% diodrast into gall bladder demonstrating a large calculus in cystic duct and several in the common bile duct (Courtesy of Dr I E Kirsh)

5 Narrowing of the common duct with proximal dilatation may be seen in benign strictures pancreatitis and carcinoma of pancreas

6 Filling defects in the common duct may be noted in intrinsic neoplasms of this structure A benign adenoma may simulate a radiolucent calculus while a malignant neoplasm may produce an irregular constriction

Figures 18 and 19 are examples of cholangiograms obtained by filling the biliary tree thru the gallbladder and through a T tube in the common duct

Summary

Indications
1. **Postcholecystectomy jaundice**
2. **Suspected biliary dyskinesia**
3. **Persistent jaundice with confusing features**
4. **Jaundice with inconclusive or incomplete surgical exploration**

Types
1. **Immediate cholangiography**
2. **Delayed cholangiography**
3. **Cholangiography through external biliary fistula**
4. **Peritoneoscopic cholangiography**
5. **Transabdominal cholangiography**

Radiopaque substances
1. **Lipiodol**
2. **Bromipin (brominol)**
3. **Diodrast (iodopyracet)**
4. **Umbrathor (25% suspension of thorium oxide)**
5. **Thorotrast (thorium oxide suspension)**
6. **Hippuran (ortho iodo hippurate)**

Technique
1. **Depends on type of procedure (see above)**
2. **Opaque substances injected into gallbladder or common duct**
3. **15 to 45 cc is aspirated before material is injected**
4. **Injection done slowly**
5. **Aseptic precautions**

Usefulness
1. **Postcholecystectomy jaundice may be clarified by locating the obstruction hepatic or post hepatic (calculus)**
2. **Biliary dyskinesia**
3. **Hepatitis with element suggestive of post hepatic jaundice**

Interpretation (Points to look for)
1. **Filling of ducts—hepatic ducts do not fill normally because of sphincter action**
2. **Size of ducts—dilatation means obstruction**
3. **Entering of opaque medium into duodenum**
4. **Oval radiopacities or radiolucencies**
5. **Narrowing indicative of stricture**
6. **Filling defects indicate neoplasm**

Calculi of Hepatic Ducts

Calculi in the hepatic ducts are secondary to cholecystitis They usually find their way up there after surgical manipulation These calculi which may be displaced upward during cholecystectomy and manipulation of the common duct may later find their way down into the common duct resulting in its obstruction It is imperative therefore when clearing the common bile duct of stones to prevent their displacement into the hepatic ducts and probe for them before the biliary passages are closed Cholangiography is of help in locating calculi in the hepatic ducts but it must be kept in mind that the sphincter of the hepatic duct may prevent the radiopaque medium from going into these ducts and give an illusion of a calculus

Hepatic Calculi

Calculi in the liver itself are not important from the point of view of differential diagnosis of jaundice since they do not produce icterus It is appropriate to discuss them here since in about 6% of cases cholelithiasis is associated with hepatic calculi if they are carefully searched for (Ba ler and Peters) Hepatic calculi were reported by Keech in a patient with primary carcinoma of the gallbladder and metastases to the liver They are usually asymptomatic and are discovered on roentgen

ray examination The symptoms accompanying hepatic calculi are due either to the associated cholelithiasis or infection The latter may produce multiple hepatic abscesses

The treatment is conservative if the calculi are asymptomatic or is directed toward the cholelithiasis or the infection

CHOLANGITIS

Cholangitis may be classified briefly into the following subgroups according to

1 Time
   a acute
   b chronic
2 Type
   a catarrhal
   b suppurative
3 Etiology
   a primary
   b secondary

Primary Cholangitis

It may be most useful for our purposes to start this discussion with the third group Primary cholangitis is very rare when it occurs, it is practically impossible to diagnose clinically This is especially true of the suppurative variety which almost always is secondary to obstruction or stasis in the biliary ducts Acute catarrhal cholangitis or acute catarrhal jaundice is an entity that can be relegated to the *archives of medical history The condition* formerly classified under this heading and regarded as catarrhal cholangitis ascending from the duodenum is now recognized as a viral form of hepatitis The point to remember is that intrahepatic pericholangitis does occur in all cases of hepatitis as evidenced by the periportal exudative process Some still cling to the conception that primary catarrhal cholangitis with inspissated highly viscid bile may produce an obstruction of the common duct While it is impossible to state that such a situation may not on occasion take place it must be exceedingly *rare and of little clinical importance*

Chronic primary cholangitis is of interest in regard to the development of biliary cirrhosis and will be discussed in the appropriate chapter (page 435)

Secondary Cholangitis (Acute Suppurative Cholangitis)

The unobstructed biliary ducts are very resistant to infection by microorganisms this was proved experimentally many years ago Acute suppurative *cholangitis is secondary to* the following diseases interfering with the patency and integrity of the extrahepatic bile ducts

1 Choledocholithiasis
2 Carcinoma of the pancreas
3 Carcinoma of the common bile duct or papilla of Vater
4 Stricture of the common duct
5 Surgical or spontaneous fistulas between the extrahepatic bile ducts or gallbladder and some portion of the gastrointestinal tract

The facility with which cholangitis develops in this last group is also dependent to some extent on obstruction and on the length of the common duct between the anastomosis and the liver The closer the anastomosis is to the liver, the more likely is it that cholangitis will develop The frequency of cholangitis in the spontaneous fistulas depends to some extent on the portion of the gastrointestinal tract involved A cholecystocolonic or choledochocolonic fistula is more likely to result in ascending cholangitis than fistulas higher up however, I have seen two cholecystocolonic *fistulas (with regurgitation of barium from* the colon into the gallbladder) existing for years without any untoward symptoms This supports the presence of a sphincteric action in the terminal hepatic duct which prevents the intestinal content from getting into the substance of the liver

Choledocholithiasis is the commonest obstructive lesion giving rise to suppurative ascending cholangitis But the cholangitis like the obstruction is likely to be intermittent and resolve without surgical intervention

A syndrome of pseudocholedocholithiasis with pain chills and fever of cholangitis can be produced by rupture of an Echinococcus cyst into the bile ducts In addition to the above symptoms a shock like and anaphylactic state develops and marked eosinophilia may be pres

ent Atlas and Kamenear recently reported two such cases

Carcinoma of the pancreas is an uncommon cause of suppurative cholangitis but one to be reckoned with Carcinoma of the common duct of the pancreas and papilla of Vater may result in suppurative cholangitis after obstructing the common duct

Strictures of the common duct as well as the hepatic duct give rise to suppurative cholangitis sooner or later The strictures usually follow trauma to the duct surgical trauma is most common but stab wounds or gun shot wound will occasionally be responsible The rapidity with which cholangitis develop after stricture formation depends on the presence and degree of the inflammatory process at the time the stricture develops But even a stricture in a sterile field would eventually invite the ascent of micro organisms from the gastrointestinal tract or their invasion of the ducts from the blood stream

Cholangitis and obstruction may be simultaneous processes with the duct becoming obstructed as it becomes inflamed The inflammation may extend from an adjacent abscess through the wall of the duct thus producing an inflammatory obstruction Choledochitis with post hepatic jaundice has been reported as occurring in patients with ulcerative colitis (Lahey Clinic) Such an inflammation arising in the absence of a mechanical obstruction may produce a type of obliterating choledochitis The obliterating intrahepatic cholangitis observed by Klemperer originates intrahepatically is not suppurative in nature and may be a predecessor of primary biliary cirrhosis (Chapter 58)

Benign common duct stricture due to surgical trauma is the commonest cause of extrahepatic biliary duct stenosis It was responsible for common duct obstruction in 65% of a group of cases studied by O Malley and associates Some of these patients gave a history of multiple operations The duct may be compromised by inadvertent clamping ligature or incision The stenosis may result from an inflammatory process (Graham 1947 Hawkins and associates 1952) Cicatricial or inflammatory stenosis results in intermittent or continuous post hepatic jaundice intermingled with attacks of chills and fever indicative of cholangitis The cholangitis may be catarrhal and if oft repeated and unrelieved may lead to biliary cirrhosis (Chapter 58) If the cholangitis is suppurative multiple hepatic abscesses may result

Congenital atresia of biliary ducts This is a rare congenital anomaly which most frequently terminates in biliary cirrhosis and liver failure (see p 433) but occasionally suppuration may occur While it is a rare lesion it is the commonest cause of surgical jaundice in infants Twenty five cases or 61% of those reported by Gerrish and Cole showed this lesion (Table 21)

TABLE 21

Surgical Jaundice in Infants and Children

Age [illegible]		No.	%
1 to 42 days	Congenital atresia of biliary tract	25	61
m s to 10 yrs	Congenital hemolytic ic[illegible]ter	9	
1 to 3 days	Inspissated bile m cous plug		7 3
to [illegible] yrs	Inflammatory stricture of bil ducts	2	4 9
10 d y	Cystic dilatation of common duct	1	4
7 days	Duodenal diaphragm oc l ampulla	1	2 4

Cholelithiasis present in one case
From Gerrish and Cole Arch Surg 63 9 1951

The pathogenesis is thought by some to be based on intrauterine obliterative cholangitis but a more likely explanation is that it is a congenital malformation or agenesis such as cardiac malformations polycystic kidney polydactylism multiple spleens agenesis of cystic duct absence of gallbladder or conversion of this structure into a mucous cyst

The clinical picture is that of progressive icterus beginning several days after birth with acholic stools and absence of urobilinogen but with abundance of bilirubin in the urine Occasionally some urobilinogen has appeared in the stool because of incomplete obstruction The liver and spleen are enlarged and ascites and edema develop terminally Signs and symp-

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toms of sepsis supervene when infection invades the biliary tree Without surgical intervention, life rarely extends beyond six months Some *infants living for three years and longer probably* had some permeability of the biliary ducts It is difficult to distinguish this anomaly from *acute hepatitis of the newborn* Surgical exploration may have to be resorted to

The laboratory findings are those of posthepatic jaundice with the exception of the alkaline phosphatase which does not become elevated

Congenital cystic dilatation of extrahepatic bile ducts This too is a rare anomaly which characteristically affects females The symptoms begin before the age of 10 and consist of bouts of pain jaundice fever and a palpable tumor in the right hypochondrium The tumor may vary in size and may be accompanied by a dilated gallbladder and compress the stomach and duodenum The variability of the size and especially the increase of size after a meal may *suggest the diagnosis*

Suppurative cholangitis may arise secondarily to systemic diseases such as typhoid fever or pneumococcic and streptococcic septicemias It is likely that under those circumstances there is involvement of the liver primarily and the larger bile ducts are involved secondarily in other words a descending cholangitis develops

Cholangitis lenta This term is applied to a systemic infection with Streptococcus viridans in which the central focus of involvement is the liver rather than the heart It is not a well defined entity and may be a suppurative process *in the liver secondary to disease elsewhere or to* neoplastic or calculous disease of the biliary tract A streptococcic septicemia may occur however secondarily to an inflammatory process due to this organism in the gallbladder or bile ducts A Streptococcus viridans bacteremia in a jaundiced patient should therefore be suspected as of hepatobiliary origin

Bacteriology of suppurative cholangitis The bacteria responsible for suppurative cholangitis include a variety of organisms Escherichia coli is probably the organism most frequently isolated however enterococci are also frequently found The organisms responsible for the infection depend somewhat on their origin that is whether they come from the gastrointestinal tract or are blood borne Pneumococci streptococci staphylococci typhoid and paratyphoid bacilli are also responsible for cholangitis

Clinical features of suppurative cholangitis The clinical features of suppurative cholangitis are those of sepsis with some localization to the right hypochondrium The clinical and laboratory findings may *simulate pyogenic liver* abscess a condition that is a frequent sequela of purulent cholangitis Since cholangitis is so frequently preceded by common duct obstruction jaundice is a commoner finding and is likely to be deeper in cholangitis and cholangitic abscess than in pylephlebitic abscess of liver The jaundice may wax and wane with the severity of the infection since spontaneous drainage of the biliary tree as in choledocholithiasis would drain the infected bile ducts

The past history may suggest cholelithiasis or trauma to the common duct or other conditions *likely to produce obstruction of the* common duct while there is an absence of other intra abdominal conditions such as appendicitis that could contribute to other types of pyogenic liver abscess (Chapter 26)

Chills a septic fever curve and drenching sweats during defervescence are accompanied by anorexia nausea and occasional vomiting Pain may be confined to the right hypochondrium or may occur throughout the upper abdomen The liver becomes enlarged and tender and the spleen becomes palpable The severity of the septic symptoms and the enlargement of the liver and spleen may help to distinguish the suppurative form from nonsuppurative cholangitis

The jaundice may be very intense and indicate complete exclusion of bile from the intestine Evidence of liver damage may appear early because of the spread of the diffuse inflammatory process into the hepatic parenchyma

Leukocytosis is marked and increases with the formation of a liver abscess The blood stream may *become secondarily infected* Gamma globulin rises early but flocculation tests remain negative

The differentiation of this condition from empyema of the gallbladder may be difficult or

impossible Indeed the cholangitis may follow empyema of the gallbladder In general the signs of sepsis and jaundice are more marked in cholangitis A palpable gallbladder calls attention to the likelihood of primary gallbladder disease however in cholangitis secondary to carcinoma of the pancreas a palpable gall bladder may be found

Duodenal drainage may help to establish the diagnosis by revealing clumps of pus cells and bacteria as well as cholesterol crystals and calcium bilirubinate If the obstruction is complete the content of the biliary ducts may not reach the duodenum Blood in duodenal drainage or tumor cells would indicate the presence of malignant obstruction

A flat x ray of the abdomen may reveal the presence of biliary calculi Elevation of the right diaphragm is not to be expected in this disease and if present would suggest the presence of a large hepatic abscess (Chapter 27)

Summary

History
- Cholelithiasis
- Trauma
- Surgery
- Other causes of obstruction

Symptoms
- Chills
- Septic fever
- Drenching sweats
- Anorexia
- Nausea
- Vomiting
- Pain right hypochondrium

Findings
- Jaundice which may wax and wane
- Liver enlarged and tender
- Spleen enlarged

Laboratory
- Leukocytosis marked
- Evidence of post hepatic icterus
- Gamma globulin rises early but flocculation tests remain negative

The Role of the Liver in Diseases of the Gallbladder and Bile Ducts

The question of the effect on the liver of diseases of the extrahepatic biliary passages has two important aspects The first deals with the development of hepatic abnormalities secondary to extrahepatic biliary tract disease and the second deals with the diagnostic complexities resulting from liver injury in such instances In post hepatic jaundice the distinctive physiologic abnormality is the exclusion of bile from the gastrointestinal tract if this alone is present post hepatic or surgical jaundice is easily established But in clinical medicine nothing comes that easily Superimposed hepatic injury results in clinical and laboratory evidence pointing to hepatic (medical) jaundice The final conclusion therefore must depend upon an evaluation and proper appraisal of all of the evidence so that the correct inference may be drawn

Pathogenesis of Liver Injury

Two factors are operative in the production of liver injury in post hepatic jaundice (1) biliary obstruction (cholangiostatic factor) and ( ) infection ascending cholangitis (cholangitic factor) The first of these may be referred to as producing biliary hepatitis and the second one purulent hepatitis

In biliary hepatiti the commoner of the two forms injury is due to increased pressure in the intrahepatic ductal system and the chemical irritating effect of the regurgitated bile In the extreme form the increased pressure may result in dilatation of the intrahepatic ducts hydrohepatosis These cystic dilatations exert pressure on the parenchyma and on the adjacent vascular channels with resultant ischemia For that reason some of the parenchymal injury may be on a vascular basis Bile casts and bile thrombi are formed mainly in the central zone The larger bile ducts are over distended with bile and there is evidence of bile duct proliferation The pronounced evidence of biliary stasis is out of proportion to the minimal parenchymal damage Parenchymal changes develop later when focal necrosis (bile necrosis) of groups of cells that have imbibed much bile are seen The Kupffer cells become laden with bile and proliferate

In the more advanced cases some periportal fibrosi is seen which eventually progresses into distortion of the lobular pattern and pro-

duction of biliary cirrhosis (Chapter 58) Roholm and Krarup s serial needle biopsy studies demonstrate the salient histologic alterations in post hepatic jaundice Their data point out the lack of correlation between the degree of parenchymatous changes and dura tion of jaundice There is some correlation between fibrosis and duration of jaundice The table presented by Weisbrod and associates is useful in differentiating between hepatitis and post hepatic jaundice (Table 18)

The great variation in the rate of hepatic damage suggests that other less well defined factors are operative in the final result It can be safely conjectured that the state of the liver especially its circulation and nutrition is im portant in regard to the rapidity with which parenchymal changes develop The classical experiment reported by Dostal and Andrews of 161½ months survival of a dog with complete biliary obstruction shows how resistant the liver may be to this type of injury Infants with congenital biliary atresia may survive for two or three years and Hawkins and co workers recently reported a case of a 62 year old woman who survived for 13 months after complete obliterative extrahepatic cholangitis which followed surgery

TABLE 2

Results of the Intravenous Galactose Test and of the Prothrombin Response to Vitamin K in 188 Patients with Obstructi e or Parenchymatous Jaundice

Tyt (J d	N f	I V g l t t st		P th mb sp t l m K	
		L nd 0 m cr	Ov 0 mg cr	P t cr	Vega t cr
Obstructive jaund ce					
All cases	86	82	18	91	9
Uncomplicated cases	68	95	5		
Parenchymatous jaundice					
All cases†	10	4	76	4	96
Ict ric index over 50 U	80	4	96		

Including cases with b liary cirrhosis

† Includ ng cases with jaundice which was slight (ic teric index under 50 U) or of short duration

T L Althausen Liver Function Tests in the Differ ential Diagnosis of Jaund ce Am J Med 4 208 1948

In general patients who have been suffering from biliary disease for years are not likely to begin their obstructive episode with a com pletely intact liver therefore evidence of liver damage is likely to become evident after one or two weeks I have seen a patient die after four weeks of obstruction of the common duct with progressive hepatic failure and azotemia (Case 2 p 107)

While the severe infectious sequela of ob struction (purulent hepatitis) is a less com mon cause of liver damage in obstruction it is more serious since it is added to the mechanical factor Moreover an inflammatory process short of a purulent process probably exists in all cases of obstruction and may even precede the obstruction A mild periportal exudative process occurs in obstruction of the common duct in the absence of suppurative cholangitis

Laboratory Evidence of Hepatic Injury

While the clinician depends a good deal on the laboratory to differentiate hepatic from *post hepatic icterus* abnormal liver function tests are frequently found in patients with biliary tract disease Cantarow found impaired hepatic function in 44 8% of 138 patients with calculous cholecystitis and in 83 7% of patients with common duct stone Since many of these patients were jaundiced and the B S P was the most important test this data must be inter preted with caution Betty and Gray found abnormal colloidal gold tests in 367% of

TABLE 3

Flocculation Tests and Alkaline Phosphatase in Post hepatic Ja nd ce

D e	N f p t t	N with phs l fl l t g t th 1+	N u th thym l t b d t g t th 5 0 p cc	N w th lk l pho phat f 5 10 B d ky t	N with lkal e ph ph t f 10-15 B d ky ts	N with lkal pho phat g t th 1 B d ky t
Carcinoma	5	6	10	1	6	18
Gallstone	0	6	7		5	13
Stricture	3	1	1	0	0	3
Totals	48	13	18	3	11	34

From Mellinkoff Tumulty and Harvey The Differ entiation of Parenchymal Liver Disease and Mechanic l B liary Obstruct on New England J Med 246 7 9 195

patients with quiescent biliary tract disease and in 58 8% of patients exhibiting evidence of infection and jaundice The first of these figures is interesting and important since it points to hepatic injury before duct obstruction takes place Meyer and co workers found 59 of their 95 patients with surgical jaundice having impaired liver function tests and pointed out that malignant obstruction is more likely to disturb liver function than benign obstruction The colloidal red and intravenous galactose tests are occasionally found positive in post hepatic jaundice (Table --) The thymol turbidity and cephalin cholesterol flocculation tests are also occasionally positive in mechanical obstruction (Table 23)

Some very interesting and pertinent data about the effect of gallbladder disease on the liver has been presented by Mateer and co workers In a study of 13 surgically treated patients with cholelithiasis histological and biochemical abnormalities of the liver were detected in most of them (Table -4) Jaundice was uncommon in these patients and grossly the livers looked normal Only 6% showed histologically normal livers while 33% had microscopic periportal cirrhosis and 15% acute infiltrative hepatitis

One or more liver function tests were positive in 6 % of this group The sulfobromophthalein test the most frequently positive test was abnormal in 34% of cases It was not performed in jaundiced patients Increased urinary uro bilinogen was next in sensitivity and was positive in 28% of cases One of the flocculation tests was positive in 15% or less

These accumulated observations point to two conclusions (1) extrahepatic biliary tract disease has a deleterious effect on the liver and ( ) isolated abnormal liver function tests are not conclusive evidence of primary hepatic disease or hepatic jaundice From both the therapeutic and the diagnostic point of view decisions should be reached early in the disease to be valid and effective

Tumors of the Gallbladder

Benign Tumors

Benign tumors of the gallbladder are rarely productive of symptoms and are of no impor

TABLE 4

Results of Various Liver Funct on Tests in 132 Cases of Choleth asis and 31 Cas s of Peptic Ulcer (D odenal 7 Gastric and 2 Jejunal Ulcers)

Type f T t Empl y d‡	*p t t ted G* St	Ul	*f po t t t† G* St	Ul er
Broms lphale n test (45 min 5 mg per kilo photo meth od)§	82	6	34	38
Ceph l n ch lester l flocc la t on te t	123	31	13	6
Thymol turb dity t st (red ced pH of 7 55 d ubling s nsi t vity)‖	123	31	13	13
Thymol flocc l t n test	121	31	1	1
E ther thymol turbid ty or flocc l t on t st or both positiv	1 3	31	15	16
Q titativ urina y urob l no-gen t st (2 hr collect on f urine)	/	11	8	9
Ser m alb m n res lts	74	3	16	1
Blood pr thromb n (q ck—norm l standard—r ad ng bo e 50%)	109	7	1	0 0
% of p tients with o e or m re po t ve tests			6	48
% of patie ts with two o m re positi e test			9	6¶

* A erag of 4 4 test d ne o a h pat ent (583 t sts 1 2 p t ent)

† N acc r t ded t on c be d wn f om th table bout r l t e ns ti ity f test Six test n t d e on all id ntical cases

‡ Ulcer gr p of 1 wer s s l ss ig fica t st t s t c lly

§ B S P t st w ot co d ted on ja d ced pati nts

‖ Thym l t rb d ty r ults bo e nits are po iti e

¶ From J G Mateer C mb d L er B op y a d L er F ctio St dy n 132 C es of Cholelith a i and 31 C es of Peptic Ulcer C t o nt ology 11 8 1948

tance in the differential diagnosis of jaundice since their fixed position prevents them from obstructing the common duct The types of benign tumors found include fibromas lipomas myomas myxomas and mixed tumors which are very rare Papillomas however are com mon and have been found in 8% of surgically removed gallbladders (Walters and Snell) Wellbrock found 69 adenomyomas in 9 550 surgically extirpated gallbladders all except four were in the fundus

The clinician may become aware of the

to areas of necrosis in the tumor but low grade infection is a contributory factor

Ascites may occur owing to peritoneal metastasis but it is an uncommon finding

Laboratory Findings

X ray is of little value in the diagnosis of carcinoma of the gallbladder Usually there is nonvisualization because of poor *concentration of the dye Radiopaque calculi may be seen* which confirm the clinical impression of cholelithiasis

Duodenal drainage may aid the diagnosis if blood is found in the aspirate and may indicate the presence of carcinoma if neoplastic cells are found however the cells would hardly be distinctive enough to enable one to determine the organ primarily involved i e pancreas ampulla of Vater or common bile duct

Anemia would be a helpful feature in distinguishing this disease from benign gallbladder disease but it occurs in a minority of cases In Lam s series only 15% had anemia and only six of our patients (24%) showed an erythrocyte count under 4 million Only one of these had severe anemia (2 4 million red cells) Leukocytosis is commoner 9 or 36% of our group had a leukocyte count of over 11 000 and two of these had counts above 20 000 One patient with a leukocyte count of 26 000 showed an eosinophil level of 22% This was interpreted as being due to the widespread metastasis The leukocytosis and lack of anemia must be interpreted in the light of the patient s hydration

Liver function test In the icteric patients hyperbilirubinemia bilirubinuria and acholic stools are observed The flocculation tests were normal in all our patients in whom they were performed Two of the patients had low total protein *(5 3 and 5.4 gm %) Alkaline phos*phatase may be increased in the anicteric patients because of liver metastasis The serum *total cholesterol* may become elevated as in one of our patients in whom it was 312 mg % The total cholesterol rarely and the esters occasionally decrease A total cholesterol of 32 mg with 32% esters and a drop of the esters to 0 in one case was observed terminally This disturbance in cholesterol metabolism is prob*ably dependent on the damage to the liver by* the metastatic neoplasm added to the preexisting damage from the chronic cholecystitic disease

Summary

Incidence
- **3% of all malignant lesions**
- **8 to 10% of malignant lesions in females**
- ***3 to 5% of patients with cholelithiasis***

Age
- **36 to 86—many over 70 years of age**

Sex
- **Four times commoner among females**

Role of Cholelithiasis
- **75% of patients have cholelithiasis**
- ***Over the age of 70 10%* of diseased gall bladders are the seat of carcinoma**

Carcinogenicity
- ***Nonspecific irritation***
- **Carcinogenic agent in calculi**

Symptoms
- **Gallbladder dyspepsia**
- **Colic**
- **Anorexia nausea vomiting**
- **Weight loss**
- **Jaundice may be mild or very marked with complete biliary obstruction**
- **Dyspeptic symptoms and pain may be of long duration**

Physical Findings
- **Palpable mass in 50% of patients**
- **Tenderness—right hypochondrium**
- **Fever—frequent**
- **Ascites—uncommon**

Laboratory Findings
- **X ray**
  - **Radiopaque calculi may be seen on plain film**
  - **Dye is not concentrated**
- **Duodenal drainage**
  - ***Blood***
  - **Neoplastic cells**
- **Blood Count**
  - **Anemia—$\frac{1}{4}$ of patients**
  - **Leukocytosis—$\frac{1}{3}$ of patients**
  - **Eosinophilia occasionally**
- **Liver Function Tests**
  - **Hyperbilirubinemia, Bilirubinuria, Acholic stools — In patients with common duct obstruction**

Alkaline phosphatase
- May be high even in absence of jaundice due to hepatic metastasis
Bromsulphalein retention may occur for same reason
Total protein may be depressed
Flocculation tests usually normal
Total cholesterol may be elevated in obstruction
Cholesterol—free and esterified may be decreased

TUMORS OF I LE DUCTS

Tumors of b le ducts can be d v ded nto ben gn and mal gant and accord ng to s te nto tumors of common b le duct cyst c duct and hepat c duct The cl n cal features depend a good deal upon the r locat on th s s e pe ally true of the ben gn tumors wh ch result in jau l ce only when they are s tuated n the common b le du t

Ben g Tumors

Ben gn tun rs are very un ommon and con s t of pap llo nas adenon as adenofibron as fibron as l po nas and adenon yofibromas They may be s ngle or mult ple c st c or sol d Marshall fo nd only four ben gn b le d ct t mors n a per od of o ears at the Mayo Cl n c Chr tophe s find ng of only 41 cases n the l te atu e up to 933 s s gn ficant When the neoplasm n the common l ct t produces a complete obstruct on to the flow of b le even when t s very small The symptoms are und st ngu shable from those of calculous ob tru t on wl ch s the d agnos s nvar ably ma le The other l n cal factor of s gn ficance s tl at they ma be precur ors of mal gnant neoplas ns

Mal ant T n ors of B le D cts

We refer here to mal gnant les ons of the larger extrahepat c b le ducts s nce ntral epat c l le duct tun ors cholang on as are d cus ed n Chapter 18 under tumors of the l ver Me enchymal mal gnant tun ors (sarcon as) of the b le ducts mu t be n e l cal cur os t es ndee l s nce I have seen no reference to s ch ca es n e ther n onograp hs r the per od cal l terature I shall therefore d scuss only carc nomas Tumors s tuated in the common duct above ts entrance nto the duodenum as well as tho e of the cyst c and hepat c ducts w ll be dealt w th Ampullary carc non as carc no nas of duodenum pancreat c carc noma are d s cus ed elsewhere It should also be stated that a carc noma nvol ng th s reg on may present insurmountable d fficult es in the determ na t on of exact s te of or g n e ther at surgery or at autopsy

Incidence It s not a fre juently en ountered neoplasm Rolleston and McNee collected 11 cases from the l te ature up to 19 9 and Marshall found 34 cases n o years at Mayo Cl n c There s a d fference of op n on as to the relat ve frequency of ductal and cholecyst carc noma Accord ng to Renshaw t s about one fourth as common as carc noma of the gall bladde wh le Wood est mates that t s more frequent represent ng about 35% of all mal gnant les ons and the gal bladder only 30 of all mal gnant les ons

Site The commonest locat on for ductal carc noma s at the junct on of the c st c hepat c and com non ducts or n the common duct ju t below tl at po nt Follow ng s a break down of the locat ons reported b Rollesto and McNee and Marshall

	R M	nd M ksll
Comm n b d	34	
Jun tion f c c mm n nd h p duc	28	
C mmon h pa c d	9	3
C d c		5
R ght and l f h a duc	4	4

It can be seen from the locat on of mo t of these neoplasms that they promptly result in complete ob truct on of the flow of b le nto the ntest nes Tl ose th t nvolve pr mar ly the cyst c or one hepat c duct pread to nvolve the other hep t c duct or common b le duct In one of Marshall s cases n wh ch the tu nor arose in the left hep t c duct marked hydrohep t os s and atroph y of the left lobe of the l ver resulted

Type of tumor Grossly three types of tumors have been descr bed (1) v ll us ( ) d ff se and (3) nodular or annular The an nular type may be confused w th a ben gn str cture H stolog cally the tumor s u ually an

adenocarcinoma with columnar or cylindrical cells and a good deal of fibrotic reaction The degree of malignancy has been graded as 3 or greater in Broder s classification in the majority of cases (Judd and Gray)

Age and sex Like carcinoma of the gall bladder the neoplasm is commonest in patients over 50 However it does occur in younger persons one of Marshall s patients was 23 It differs from carcinoma of the gallbladder in its predominance in male patients about 60% occurring in males This sex predilection suggests the lesser importance of calculi in the pathogenesis of this tumor While calculi do occur here they are not as frequent as in gall bladder cancer having been found in only 22% of 264 cases (Ewing)

Symptoms and signs Jaundice is the outstanding symptom and finding in this disease and may bring the patient to the physician Unlike carcinoma of the pancreas pain may be completely absent for a period of time while the jaundice is progressing The jaundice is unremitting and is due to complete duct obstruction in 90% of cases The skin has a greenish tint (biliverdin) as in pancreatic carcinoma and is accompanied by pruritus

Pain unlike jaundice is not severe constant or invariably present Pain may be absent completely in nearly half the patients or may begin late in the disease Biliary colic type of pain is rare and when it occurs is usually due to cholelithiasis The dull aching pain is commonest in the epigastrium and in the right hypochondrium Dyspepsia of a nondescript variety may be complained of

Weight loss may be an outstanding symptom and is important because it suggests malignant disease The majority of Marshall s patients showed a weight loss averaging 22 4 pounds (10 kilograms)

Palpable gallbladder is observed in half to one third of cases and is always absent when the tumor is situated in the hepatic ducts The gallbladder is smooth and cystic to palpation a in carcinoma of the pancreas

Hepatic enlargement may be due to the obstruction of the duct and to hepatic metastasis Gross nodularity of the liver is detected in the latter case

Chills and fever (signs of cholangitis) are common in ampullary tumors but uncomm in tumors higher up When they do occur co comitant cholelithiasis may be present

Hemorrhagic tendencies are probably due hypoprothrombinemia caused by nonabsor tion of vitamin K

Laboratory findings Laboratory tests ind cate complete biliary obstruction of the pos hepatic type but evidence of some hepat parenchymal disturbance may be elicited whe the jaundice has persisted for a considerab period of time Hypoprothrombinemia shoul respond to parenteral use of vitamin K

Occult blood in stool or duodenal drainage rare Anemia may be present because of th hemorrhagic tendency Leukocytosis may b present if cholangitis complicates the picture

Summary

Incidence about one fourth as commo as gallbladder carcinoma
Site commonest is at the junction o cystic hepatic and common ducts
Age over 50 years
Sex 60% in males
Calculi in 24% of cases
Symptoms and Signs
- **Jaundice may be first symptom—pro gressive and unrelenting**
- **Pruritus present**
- **Pain may be absent or mild**
- **Weight loss**
- **Palpable gallbladder—50% of cases**
- **Hepatomegaly due to duct obstruction or metastasis**
- **Chills and fever common in tumors near the ampulla but uncommon in tumors higher up**
- **Hemorrhagic tendencies due to hypo prothrombinemia malabsorption of vitamin K**

Laboratory Findings
- **Classical for post hepatic jaundice**
- **Stools—occult blood rare**
- **Anemia may be present**
- **Leukocytosis—due to cholangitis**

Compression of Bile Ducts by Extrinsic Mass

Obstruction of the extrahepatic ducts es pecially the common bile duct may occur from

lymph node enlargement due to extrinsic neoplastic or inflammatory causes The lymph node enlargement may be due to (1) metastatic neoplasm (2) blood dyscrasias or lymphomas such as lymphatic leukemia (Bower 1951) Hodgkin s disease myelogenous leukemia or follicular hyperplasia of lymph nodes or (3) inflammatory lesions of lymph nodes such as tuberculosis and syphilis All these conditions can and do involve the hepatic parenchyma and therefore may produce hepatic jaundice If the primary disease has been established the differential diagnosis of the type of jaundice is not so critical since the primary disease is a medical therapeutic problem anyway The only exception to this is metastatic neoplasm in which surgery for relief of the extrahepatic obstruction may be undertaken for palliative purposes Post hepatic jaundice due to obstruction of the common bile duct was recently reported as the presenting symptom in bronchogenic carcinoma (Berkowitz and co workers 1952)

Examination of the stools for bile pigments and the palpatory findings of the liver may enable one to make this differentiation Acholic stools indicate bile duct obstruction and a grossly nodular liver indicates hepatic metastasis *If both of these findings are positive the* diagnosis is post hepatic jaundice due to metastatic neoplasm Needle liver biopsy may likewise be of great help in detecting the hepatic metastasis

17 — *Clinical and Laboratory Features of Post-Hepatic Jaundice Due to Neoplasms Originating Around the Common Bile Duct*

PANCREATIC CARCINOMA

WHILE pancreatic carcinoma is uncommon (about 5 % of all malignant lesions) when it occurs it frequently produces posthepatic jaundice and must be considered in the differential diagnosis in all cases of biliary obstruction In 400 cases with jaundice analyzed by Bachrauker and Gilbert 43 % were due to malignant disease and 53 % of the malignant lesions causing common duct obstruction were carcinomas of the pancreas (Tables 6 and 7) In other words carcinoma of the pancreas is a leading cause of post hepatic jaundice Jaundice is produced most commonly when the head of the gland is the seat of the neoplasm and in these cases jaundice is present in about 68 % of patients Primary pancreatic carcinoma less commonly arises in the body and tail of the pancreas and jaundice while less frequent occurs in nearly one fourth of the patients (Smith and Albright)

The average patient with this disease is in the sixth decade It is very rare in young persons but has been observed in adolescents and even infants Age is of some help in differentiating the disease from hepatitis Males are about three times more prone to this disease than females in contrast to the incidence in cholelithiasis

Pancreatic carcinoma has been erroneously ascribed as a cause of painless jaundice Actually pain is the commonest symptom of this disease (75 %) What was meant is that the pain is not colicky and not dramatic in its onset

TABLE 6

Causes of Jaundice and Frequency in 400 Patients

	Total	Per Cent
Malignancy	175	43 75
Common duct stone	86	1 50
Inflammatory	64	16 00
Hemolytic	38	9 50
Portal cirrhosis	0	5 00
Unknown	11	75
Stricture	6	1 50
	400	100 00

Includes two patients with Hodgkin s disease

C A Bachhuber and A E Gilbert Four Hundred Consecutive Cases of Jaundice Am J Surg 76 144-149 1948

TABLE 7

Relative Frequency of Various Malignant Neoplasms Causing Obstruction of the Common Duct

	Total	Per Cent of Malignancy	Per Cent of Total
Carcinoma of head of the pancreas	94	53 71	3 50
Carcinoma of biliary tract			
Gallbladder ducts and papilla of Vater	36	0 57	9 00
Metastatic carcinoma to liver	3	18 9	8 00
Pressure on duct (2 cases of Hodgkin disease)	12	6 86	00
Carcinoma of duodenum	1	57	c
	175	100 00	43 75

C A Bachhuber and A E Gilbert Four Hundred Consecutive Cases of Jaundice Am J Surg 76 144-149 1948

as in calculous obstruction of the common duct *The pain varies in location character and ex*tension in individual patients and according to location of the tumor It is usually epigastric dull *aching and steady Extension of the pain* to the back its aggravation in the supine position and relief obtained by patients by sitting *up or leaning* forward are characteristic of pancreatic carcinoma It is more likely to show these characteristics in carcinoma of the body or tail but is present with involvement of the head of the pancreas as well Loss of weight is an important feature in this condition Fever has been reported in as high as 26% of cases (Brown and collaborators)

Jaundice once developed is constant and progressive and becomes very deep A green *discoloration of the* skin is characteristic and is probably due to the increased biliverdin Pruritus is commonly present Palpation of a *mass in the region of the* pancreas is a helpful sign A distended gallbladder may be palpable according to Courvoisier s law this is a sign of *neoplastic obstruction I have* observed a palpable gallbladder in calculous obstruction so that while this sign is suggestive it is not entirely *diagnostic of neoplasm*

Multiple venous thrombi are a frequent complication of carcinoma of the body and tail of the pancreas perhaps by *virtue of an ac*celerated clotting mechanism due to trypsin or some unknown substance

Laboratory tests characteristically show normal hepatic function and complete exclusion of bile from the gastrointestinal tract The total serum cholesterol is elevated and the percentage of esters may be decreased Serum lipase is found elevated more frequently than the serum amylase especially when the tests are done serially A study of the duodenal enzymes after stimulation with secretin was found helpful by Nothman The external pancreatic secretion shows a reduction in volume in bicarbonate and a decrease or absence of enzymes after secretin stimulation This is due to obstruction of the pancreatic duct by a neoplasm in the head of the gland One can visualize some danger in this test if the stimulation of the gland with an obstructed *duct* results in pancreatic edema The serum enzymes may become elevated after stimulation with *secretin if the gland is not destroyed by tumor* A rise in serum amylase and lipase has been noted by Lopusniak and Bockus after intravenous injection of 80 units of Wyeth s secretin

A markedly elevated plasma antithrombin titer in jaundiced patients with carcinoma of the pancreas has recently been reported by Innerfield and Angrist They found the antithrombin activity increased in 11 patients with carcinoma of the pancreas with jaundice of less than four weeks duration This titer was low in one patient with carcinoma of the pancreas with extensive hepatic metastasis and *normal* values were found in 109 of 113 patients with other types of post hepatic jaundice This test

may prove to be of great value in the diagnosis of this disease if this promising observation is extended to a larger number of cases

An elevated blood sugar level may precede or follow the development of carcinoma of the pancreas Marble found an increased incidence of carcinoma of the pancreas in diabetics which is in accord with my casual observations On the other hand glycosuria may develop secondarily to the destruction of the gland Abnormal glucose tolerance may be detected in the presence of a normal fasting blood sugar level

The stools show diagnostic features in carcinoma of the pancreas and may give a clue to the diagnosis even on gross inspection The bulkiness of the stools is impressive in pancreatic achylia indeed the largest stool weight is found in this condition The increase of the weight of the stool is due to increased fat and protein which escaped digestion and absorption The oily and fatty appearance of the stool can be readily detected by inspection when the patient has been on a diet containing an abundance of fat (Brown and co workers) This simple procedure of gross inspection should not be neglected for it may help the diagnosis immeasurably If the stool is solid it should be cut with a knife for the butter like masses may be in the interior

If the gross examination is not conclusive chemical analysis for fat should be done after the patient has been on a Schmidt or similar diet Nothman suggested a modified diet containing 105 gm of protein 135 gm of fat and 180 gm of carbohydrate for this purpose In a normal individual over 90% of the fat and nitrogen is absorbed Slight steatorrhea may occur on this diet in hepatic icterus as well as in calculous obstruction of the common duct The absorption of nitrogen remains normal In the complete obstruction of the pancreatic duct about 60% of the fat and 50% of the nitrogen can be recovered in the stool Microscopic examination of the stool reveal numerous meat fibers The undigested proteins and neutral fats in the stool are characteristic of pancreatic achylia

Occult blood in the stools may be found in 25% of cases That the bleeding is not severe is evidenced by the fact that anemia is usually mild and not too common Leukocytosis of mild degree has been noted but occasionally it is marked

X ray examination may contribute to the diagnosis by the following findings (1) enlargement of the duodenal loop ( ) inverted 3 deformity of the descending duodenum and (3) pressure deformity of the antrum and greater curvature of stomach

Summary

Incidence 5% of all malignant diseases commonest malignant lesion to produce **post hepatic jaundice**

Age Sixth decade

Sex Males three times as common

Symptoms

- **Jaundice in 68% of carcinoma of head of pancreas severe progressive**
- ***Pruritus***
- **Pain in 75% of patients epigastric dull aching boring steady extends to back worse in supine position relieved by leaning forward**
- **Loss of weight**
- **Palpation of mass**
- ***Gallbladder palpable***
- **Fever in one fourth of patients**
- **Venous thrombosis**

Laboratory

- **Liver function tests are normal**
- **Total cholesterol elevated**
- **Serum lipase elevated more often than Serum amylase**
- **Duodenal enzymes decreased after stimulation**
- **Plasma antithrombin titer elevated**
- **Hyperglycemia**
- **Stools**
  - **Acholic**
  - **Bulky**
  - **Oily and fatty appearance**
  - **60% of ingested fat and 50% of nitrogen can be found in stool**
  - **Occult blood in 25% of patients**
- **X ray**
  - **Widened duodenal sweep**
    - **Inverted 3 of descending duodenum**

Pressure deformity of antrum and greater curvature of stomach

Carcinoma of Ampulla of Vater

Jaundice due to carcinoma of the ampulla of Vater is often difficult to distinguish from that due to carcinoma of the pancreas on the one hand and choledocholithiasis on the other hand Pain is a constant feature in this condition and may simulate a duodenal ulcer The tendency of this neoplasm to ulcerate results in two of its diagnostic features occult blood in the stool is almost always present and the jaundice fluctuates in intensity Anemia may be severe because of the bleeding The gallbladder may be palpable while no other mass is palpable unless the neoplasm is advanced The enzyme studies are similar to those in carcinoma of the pancreas but there is no carbohydrate disturbance Intubation of the duodenum may reveal the presence of blood and tumor cells Tumor cells have also been found in carcinoma of the head of the pancreas An irregular filling defect is found on x ray after a barium meal in the region of the ampulla

Benign Tumors of Ampulla

An adenomatous polyp of the ampulla of Vater is a rare cause of a complete obstruction of the common duct A recent case has been reported by Wheelock and co workers Rogers cited 24 cases in the literature The general condition of the patient is better than in carcinoma and anemia and occult blood in the stools are not such constant features The x ray may show a perfectly smooth round defect in the duodenum

Carcinoma of Second Portion of Duodenum

Carcinoma of the second portion of the duodenum close to the ampulla of Vater may eventually involve the opening of the common bile duct by extension The diagnostic features of this lesion which help in distinguishing it from the ampullary carcinoma are (1) a variable period of illness before jaundice appears (2) dyspepsia and vomiting and pain and (3) more extensive changes seen roentgenographically Actually these fine distinctions are not important clinically and the differentiation may even be impossible at surgery or at autopsy when the lesion has become extensive Blood enzyme determinations should be done one and four hours after secretin injection

Cysts and Benign Tumors of the Pancreas

Cysts and benign tumors of the pancreas are uncommon and are rarely the cause of post hepatic jaundice by compression of the common bile duct Cysts with the exception of the congenital variety or neoplastic ones (cyst adenoma) are sequelae to acute pancreatitis Trauma is another etiologic factor that may be elicited in the history of patients with cysts of the pancreas The congenital variety may be accompanied by polycystic kidney liver and lung In the cysts following pancreatitis cholelithiasis may be present thus complicating the differential diagnosis of the jaundice The common duct obstruction due to a cyst is usually relatively painless however the co existent chronic hepatitis may be productive of such pain Because the cysts may reach enormous size palpatory findings may become characteristic and displacement of adjacent viscera on x ray is also of diagnostic help Cystadenoma of the pancreas may be accompanied by similar changes in the intrahepatic bile ducts (Keech)

Pancreatic Lithiasis

Pancreatic calcification (lithiasis or calculi) is one phase of chronic pancreatitis and may produce jaundice in a considerable number of the severer cases Jaundice was present in 27% of 65 cases reported by Haggard and Kirtley The jaundice may be produced by a calculus in the pancreatic duct which impinges on the common bile duct or by the extension to or chronic compression of the duct by an inflammatory process in the pancreas The severe pain simulates that of biliary colic Immoderate ingestion of alcohol is frequently elicited in the history The enzyme and metabolic features may resemble other types of chronic pancreatitis and pancreatic carcinoma Calcification in the region of the pancreas which may assume a herringbone configuration, is pathognomonic The association of gallstones may complicate the decision of the cause of the

icterus Involvement of the liver secondary to diffuse pancreatic disease may further complicate the picture This subject is discussed in Chapter 44

Chronic Pancreatitis

Long standing or repeated inflammatory episodes in the pancreas (chronic relapsing pancreatitis) may result in fibrosis and enlargement of the gland simulating clinically and on gross inspection a carcinoma of this organ When the head of the gland is involved complete obstruction of the common duct may occur (Peterson and Cole) Since many of the features attributed to carcinoma of the pancreas such as characteristic pain stool changes enzyme and carbohydrate abnormalities may also be found in this condition a differentiation may be impossible clinically as well on surgical exploration The general condition of the patient remains favorable and suggests the benignancy of the lesion Selesnick recently called attention to the frequency of jaundice in chronic relapsing pancreatitis and to the fact that rarely it may terminate in biliary cirrhosis

Acute Pancreatitis

Rarely in acute pancreatitis jaundice may occur owing to compression of the ampullary portion of the common bile duct by extension of the edema or by impingement of the inflamed pancreas The jaundice is transient it subsides quickly with recession of the pancreatitis The diagnosis should not be difficult since the onset of acute pancreatitis is usually dramatic and suggests an acute abdominal catastrophe Occasionally the symptoms may simulate a biliary colic Typically the pain is very severe upper abdominal diffuse or epigastric colicky in nature accompanied by vomiting and obstipation These symptoms suggest mechanical intestinal obstruction but the bowel sound are decreased or absent Rigidity of the abdominal muscle is present but not as severe as in peritonitis and may be confined to the upper abdomen Ecchymotic area over the buttocks and brownish discoloration over the lumbar region (Grey Turner s sign) are considered pathognomonic of acute pancreatitis Serum amylase and lipase elevation is marked and clinches the diagnosis

Annular Pancreas

This congenital anomaly of the pancreas especially when it becomes secondarily inflamed may result in obstruction of the common bile duct The correct diagnosis may be suggested by the x ray finding of an annular constriction of the second portion of duodenum with intact mucosal pattern If inflammation of the gland is present obstruction of the pancreatic duct may result in symptoms and findings referable to the disturbances in pancreatic enzyme secretion

IV. Neoplasms and Cysts of the Liver

18—*Classification of Neoplasms of the Liver, Metastatic Neoplasms of the Liver, Etiology and Pathogenesis of Primary Neoplasms*

The relationship of the liver to neoplasms has certain remarkable features which must be based on some fundamental biological factors These factors however are still shrouded in obscurity While the liver next to regional lymph nodes is the commonest site for metastatic carcinoma it forms a rare site for primary growths Malignant tumors of the liver are frequently associated with some form of liver injury (cirrhosis) There is a startling discrepancy in racial predisposition to primary carcinoma of the liver and finally dietary factors may be of etiologic importance These unique relationships will be discussed in greater detail below

Classification of Neoplasms of Liver

Warvi proposed the following classification of primary hepatic tumors this is based on histologic features

I Hepatoma
   1 Adenoma liver cell type (hepatocellular) or trabecular adenoma
   2 Carcinoma liver cell type (hepatocellular)
      (a) Carcinoma without cirrhosis occurring as a single massive growth or as multiple nodules
      (b) Carcinoma with cirrhosis almost invariably multinodular

II Cholangioma
   1 Adenoma
      (a) Solid (tubular) type
      (b) Cystadenoma (vesicular) type
   2 Carcinoma
      (a) Adenocarcinoma varying from alveolar to medullary form
      (b) Cystadenocarcinoma
      (c) Carcinoma simplex usually associated with cirrhosis of liver

III Cholangiohepatoma (mixed tumor)* exhibiting both bile duct and liver parenchyma cells

IV Tumors primary in the liver but not containing specific hepatic elements
   1 Tumors of vascular origin—hemangioma lymphangioma endothelioma
   2 Adrenal rest tumor

* The use of the term mixed tumor for this neoplasm is inadvisable and confusing because it is more commonly used in reference to mixed embryonal tumors (Wilms s tumor) described later

3 Sarcoma
4 Teratoid tumors
5 Primary (?) malignant melanoma

From a clinical point of view it may be more satisfactory to classify hepatic tumors into metastatic and primary malignant and benign This puts greater emphasis on the problems that the clinician has to consider before the patient reaches the autopsy table

Tumors of the Liver

I Malignant Neoplasms
  1 Metastatic
    (a) Carcinoma
    (b) Sarcoma
  2 Primary
    (a) Carcinoma
      1 Hepatoma (liver cell type)
      2 Cholangioma (bile duct cell type)
      3 Cholangiohepatoma (both cell types)
    (b) Sarcoma
      1 Angiosarcoma (endothelial cell sarcoma)
      2 Alveolar sarcoma
      3 Spindle cell sarcoma
      4 Round cell sarcoma
      5 Lymphosarcoma
    (c) Malignant teratoma
    (d) Mixed tumors (embryonal) (Wilms s tumor)
    (e) Melanosarcoma
II Benign neoplasms
  1 Epithelial (adenoma)
    (a) Benign hepatoma
    (b) Benign cholangioma
      1 Solid type
      2 Cystic (cystadenoma)
    (c) Benign cholangiohepatoma (hamartoma)
  2 Mesenchymal
    (a) Hemagioma
    (b) Hemangioendothelioma

METASTATIC NEOPLASMS OF LIVER

The liver is the commonest site for metastatic carcinoma therefore when neoplasm is suspected because of nodular enlargement of this organ metastasis should be considered till proved otherwise The ratio of primary to secondary carcinoma of liver is reported in some series to be as high as 1 to 64 The abdominal organs especially the stomach and colon should be searched carefully for the possible primary site This may be difficult to find because of the paucity of symptoms and the insignificant size of the primary lesion Carcinoma of the stomach especially may produce massive metastasis to the liver and result in symptoms because of the secondary growth while the primary neoplasm remains undetected even with roentgenographic studies Figure 20a shows a liver weighing 5600 gm riddled with metastatic nodules All the symptoms were referable to the hepatic involvement while the primary gastric lesion remained undetected (Fig 20b)

The detection of multiple nodules on physical examination lack of evidence of cirrhosis and the presence of occult blood in the stool indicative of gastrointestinal bleeding favor the diagnosis of secondary hepatic neoplasm Liver biopsy if positive establishes the diagnosis

Metastatic carcinoma of the liver carries a poor prognosis 85% of patients dying within a year Solomon and Kreps reported a remarkable case of metastatic carcinoma of the liver with the patient surviving 26 years after resection of a primary neoplasm in the sigmoid Malignant melanoma may produce massive metastasis to liver (Fig 1)

Sarcomas of the intra abdominal organs are much rarer than carcinoma and when they do occur rarely metastasize to the liver Thus of 10 cases of gastric lymphosarcoma reported by Spellberg and Zivin no hepatic metastases were found even at autopsy

PRIMARY CARCINOMA OF THE LIVER

Incidence

From a perusal of Table 28 one can see that primary carcinoma of the liver is an uncommon disease The incidence of this tumor in the various autopsy series is between 0 083% and 0 (1% with two exceptions the 1% reported by Holley and Pierson and 1 87% reported by Schupbach and Chappell These are very small groups and not representative of the population as a whole

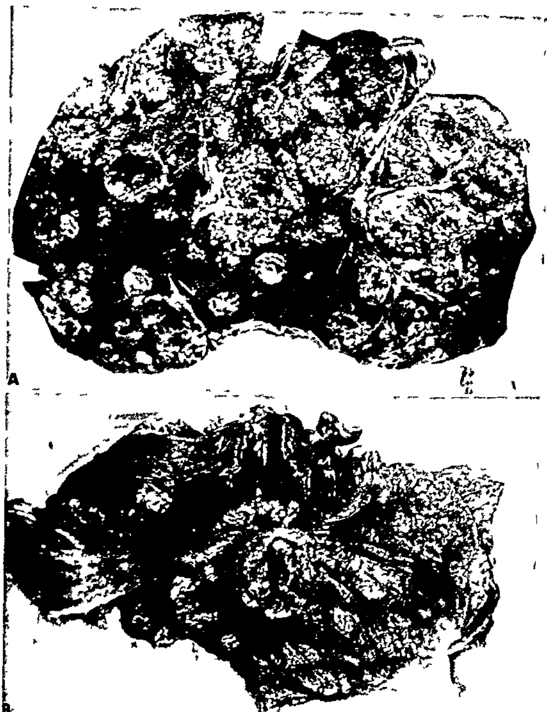


Fig o A Li r with massive meta tat c carci oma we ght 5600 gm Live p in and enlargement b ought the patient to physician
B Primary lesion in the stomach was missed roentgenograph c lly and w s small at the a topsy

In reviewing these various statistics in spite of some duplication and over lapping two points stand out 1 There is an increasing over all incidence of primary carcinoma of the liver 2 The incidence is much higher in certain races The increased incidence in more recent statistics is brought into sharp focus by comparison of statistics from the same sources



Fig 2 M gn n mel m w h m a o e The er w gh d 6000 gr m wa d k l b ue a mo bl k n co r er ha d b t fa wa ma k d nod la M c oscop e reveal d od n he l er c mp d o m l n con n ng c l w h n mero m c fig e Th m pa n ag d 4 h d a m n h l ng na g n 944 b t w w d b x ra h p a nod gh p n 946 ep ga c p n 948 Ph ex m n e d gh c he l r a g d o m bel w co al m gin a hard d la gh l end m n h r gh g al gi n ed ma f a k d crum S r m b b n 4 m m% Alka e ph ph a 2 2 B da k n C ph h e floc a n p To l pro e n 5 gram A b m n 8 gram C ob l n 5

two decades apart The Mayo Clinic group reported in 1926 (Counseller and McIndoe) an incidence of 0.083% and in collected series an incidence of 0.14% This compares with the 1947 report of Hoyne and Kernohan of 0.19% and 0.27% respectively The recent increase in incidence is also evident from the statistic of Str ng and I trs n 193 and 1949 fo the Vancouver General Hospital where in the white population the autopsy incidence was 0.109% and 0 % respectively Th it appears that the incidence of this disease has doubled in the last o years The very high incidence in two recent report (1948 and 195 has already been mentioned

A r sing incidence of primary carcinoma of the liver may be expected on the basis of increasing incidence of liver disease and cirrhosis which are precursors of this neoplasm

Berman (1951) from collected statistics concludes that the incidence of primary hepatic carcinoma in all autopsies is 0 7% in the United States and 0.14% in Europe and the incidence of this tumor among all malignancies is 5% and 1 2% respectively

Etiology

Race The predilection of this disease for certain racial groups and geographic areas is one of t most remarkable features This

TABLE 28

Incidence of Primary Carcinoma of the Liver

A tho	1	A t p	P m y No	C nom
Blatchford	1952	3 509	16	0 45
Charache	1939	159 76	808	0 506
Counseller & McIndoe	19 6	4 76 (collected)	6	0 14
		5 976 (personal)	5	0 083
Fox & Bartels	19 8	9 315	39	0 13
Fried	19 4	1 00		0 3
Holly & Pierson	1948	500	5	1 0
Hoyne & Kernohan	1947	159 144 (collected)	339 {H o	0 7
		16 303 (personal)	31 {C 11	0 19
Loesch	1939	3 000	14	0 467
McNamara et al	1950	5 400	34	0 6 9
Pack & LeFevre	1930	19 1 9		0 17
Rowen & Mallory	19 5	6 500	9	0 138
Schupbach & Chappell	195	797	14	1 87
Spatt & Grayzelle	1948	4 731	11	0 23
Strong & Pitt	1932	1 967 (mixed)	1	0 61
		139 (Chinese)	10	7 10
		1 828 (White)	2	0 109
Strong & Pitts	1949	7 340 (White)	16	0 6
		446 (Chinese)	5	5 44
		7 786 (mixed)	41	0 56
		(Total cases 55—41 H + 14 C)		
Tull	193	1 312 (Singapore)	16	1 2
Wilbur Wood & Willett	1944	11 045	49	0 44

H = Hepatoma C = Cholangioma

explains the wide variations seen in the collected series of cases Charache in 1939 collected 808 primary carcinomas in 159 762 autopsies with an incidence of 0 506% while Hoyne and Kernohan in 1947 reported only 339 carcinomas in 159 144 autopsies or 0 247% This difference is due to the fact that Charache s series included reports from African and Oriental observers from the Philippines General Hospital 1 376% Japan 2 277% and from the South African Institute for Medical Research, 39 56% primary carcinomas in all autopsies Thus it is evident that in Asiatic and in East *and South African natives the incidence is* many times that in Europeans and North Americans This predilection for colored races is seen not only in their own habitat but also *in areas to which they have migrated* Thus from Vancouver General Hospital Strong and Pitts in 1932 reported two primary carcinomas in 1828 autopsies on white persons or 0 109%, *and 10 carcinomas in 139 autopsies on Chinese* subjects or 7 19% Their 1949 report was not quite so striking but still emphasized the great preponderance among the Chinese—0 26% against 5 44%

The incidence of this neoplasm in the American Negro is not near that reported in African natives but while the statistics are not adequate the incidence seems to be higher than among the white population (Schupbach and Chappell) Moreover the American Negro is a descendant of the West African native and not of the East or South African native who show the highest incidence of this disease

While malignancies in general are less common in the colored races than in the white race *primary carcinoma of the liver* is much more common The percentage of liver carcinoma to other carcinomas in Europe and America of 1% or 2% is to be compared with *46 1% among the Javenese* 33% among the Chinese 22 2% among Filipinos 7 5% among Japanese (Berman) and 86 6% (!) in the Witwatersrand Gold Mines in South Africa *The possible explanation of this amazing inci*dence among certain racial groups will be analyzed below

Sex Th d sease predom nates n males n the rat o of 4 1 or h gher In Hoyne and Kernohan s ser es 74 ?% were males and 25 8% were females Of the 49 cases reported by W lbur et al only two were in females and of the 34 reported by Sanford four were females In the Afr can nat ves reported by Berman the rat o of n a es to fen ales was 7 1

Age In the wh te populat on th s d ease s commonest n the usual cancer age be tween 50 and 60 Among the Bantu laborers t attacks young adults It has been reported n both extremes of l fe A case has been reported n a man of 83 and W lbur Wood and W llett reported a prenatal car noma of the l er A mas was d covered n th s nfant on the th rd day of l fe and death occurred at 3 n onths Steiner rev ewed 105 cases n s bjects under 16 years of age n 75 of wh ch the d agnos s was just fied Of th s group 53 % were under the age of The sex d str but on was cur ou ly enough s n lar to that n the adult —68% n n ales an l 3 % n female Platou and H ll (1942) rep rted two add t onal case n $3\frac{1}{2}$ and month-ol l nfants Precedent l er damage does not play a part n the patho genes of th neoplasm n nfant an l t s probabl dependent or an embr on cell rest Wood howe er reported a pr mar nal gnant l epatoma n an 8 month o d female nfant suf fer ng from N en ann P ck s d sea e In sp te of ts rar ty n nfants t s p obabl the com none t carc non a n th s age group

L er Damage and Primary Carc oma of the Li er

C rrhos s

O e of the most ntr gu ng features of th s neopla m s ts freq ent asso at o w th rrho About 85% of pr mary l epato nas and 50% of p mary cl olang omas are a so ated tl c rrhos s (Ew ng) Strong et al found rho n 87 % of tl e r ent re ser es G eene n h c llected ser e foun l c rrl s n 67% of hep o ellula carc non as In Hoyne and Kernohan s er es 5% of tl e hepaton a group h d c rrl os s and onl 18 % of the cl ol n gio na g oup howe l tl s les on W ll ur and co-wo kers repo ted only 54 th c rrho n the r er es and 5 % n Sch pl a h and

TABLE 29

Inc d n of Pr ma y Ca c noma n Cas s of C rho s

Autho	C ho C	C Ca	m
Be k & L b (co l c ed) (94)	989	90	4 5
H l a (9	480	4	8 75
Loe h (939	94	4	5
M N ma a et a (H n s Ho p) 950	4	25	6
Ro n h l C k C un v H p (9 6	68	7	9 3
W b e al (S anford l n 9 4	346	49	0

Chappell s ser es wh le McNamara and co workers found c rrho s n 92% of the hepatoma group and n 8% of the cl olang oma g oup

It s al o pert nent to look at the p cture from the other po nt of v ew to see how fre quently pr n ary carcino na occurs n c rrho s Wh le there a ar at on here as well (see Table 9) th s nc dence of between 4 5% and o er 10% l ghl gn ficant

Be k and L eber er es as collecte l from the l erature up to 1941 b t the n ore recentl reporte l er e altl ough small l ow the h gher nc dence The a c at on of c rrhos s and p mar ca c n n a of the l er s further empha e l by the h gh nc den e of the e two d se ses among South Afr can nat ves G lbert and G llm an fou d c rrl o s n 80% of n ale autop es at the Johanne burg General Hos p tal as vell the h ghest nc dence of pr n ary carc noma n the wo l l

Th s clo e as o at on between tl ese two cond t ons ra es the follow ng quest ons 1 Does the c rrho precede and cau e the carc no na? Does the carc noma precede and cau e the c rrho s? 3 Are tl e two c nd t on ndependent of each other? 4 Does the san e et olog factor p oduce botl cond t ons? Wh le tl e e quest ons cannot l e answere l w th final ty there s ev dence that po nts to the n o t acceptal le nterpretat on Wl le the neoplasn nay pr duce son e local t s ue reac t on th fil ros n the imn ned ate v c n ty of the tun or it would not be expecte l to produce d ffu e changes far away from tumor t sue Thus hen the changes are d ffu e as they are n true c rrhos these changes mu t have ar en in lependently of an l probabl before

was thought by some to be due to the increased concentration of lipids in the liver Silverstone (1948), however found that the total lipid and cholesterol concentration in the liver was related neither to the rate of hepatoma development nor to the concentration of butter yellow in the liver By means of varying the diet this investigator was able to vary the incidence of hepatomas from 25% to 95% in rats

It has been pointed out that biotin (du Vigneaud et al 1942) and vitamin B_1 (Day et al 1950) enhance the carcinogenic effect of butter yellow Diet however appeared to have no influence on liver tumors in rats produced by 2 acetylaminofluorene The manner in which diet produces its procarcinogenic or anticarcinogenic effect is unknown Chemical differences between mitochondria of normal liver and mouse liver hepatoma has been reported by Hogeboom and Schneider

Some interesting observations in regard to the influence of diet on the development of spontaneous hepatomas in inbred C3H mice were made by Tannenbaum and Silverstone These investigators have shown that increase of *fat* in the diet from 2% to 20% increased the rate of hepatoma formation from 37% to 53% Low *riboflavin* intake resulted in a *decrease* of hepatoma formation This can be attributed to the lowered caloric intake which has been shown to inhibit growth of hepatomas in this species It has likewise been shown that contrary to the experiences in induced hepatomas in rats the spontaneous tumors in mice are not accelerated by a rice diet but on the contrary are accelerated by increased *casein* content *Methionine* has likewise been shown to accelerate the development of these tumors in mice The conclusion is drawn that the *sulfur containing amino acids* which are necessary for normal growth are also necessary for growth and development of these neoplasms Again a startling indication of the similarity between physiologic growth and neoplasia! These experiments in spontaneous hepatomas in mice appear to depend on entirely different dietary factors than the induced carcinomas in rats and the spontaneous human hepatomas Copper of 0 25% added to the diet exerts an inhibitory influence on the carcinogenic effect of 3 4 dimethylamino azobenzene (Pedero and Kozelka)

Primary Carcinoma of the Liver—etiology—Summary

Incidence
- **Caucasian race**
  - **United States 0 27% of autopsies 2 5% of carcinomas**
  - **Europe 0 14% of autopsies, 1 2% of carcinomas**
- **African Negro (Bantu) 86 8% of carcinomas Five times more common among South African natives**
- **Chinese 33%**
- **Japanese 7 5%**
- **Javanese 46 1%**

Sex
- **Male to female ratio 2 1 or 3 1**

Age
- **Highest incidence, 50 to 60 Occurs at both extremes of life**
- **Bantu young adults**

Etiologic Factors
- **Cirrhosis (in 85% of hepatomas and 50% of cholangiomas)**
- **Hemochromatosis**
- **Malnutrition (South Africa Orient)**

Animal Experiments
- **Carcinogenic factors**
  - **p dimethylamino azobenzene ("butter yellow")**
  - **o amino azotoluene**
  - **4 hydroxy 2 3 azotoluene**
  - **Influence of diet on above**
  - **Different effect of diet on mice and rats**

19 Pathology Clinical and Laboratory Features

Pathology

Gross

The liver is usually increased in si e and may be enormous over 7100 gm but it may be normal in size or even smaller than normal when the lesion is engrafted on a markedly atrophic liver The average weight of this organ in Berman s series was 39 5 gm Some have claimed that it is possible to distinguish grossly between the hepatocellular and cholangiocellular types This however is improbable The size multiplicity and distribution of various primary tumors have resulted in the gro s division into three groups (1) *Solitary massive tumor* in which one large nodule may occupy an entire lobe (Fig 2) This is the second commonest group ( ) *Multiple nodular tumors* which consist of many discrete nodules several millimeters to several centimeters in diameter This is the commonest group (3) *Diffuse* in which the entire liver may be riddled with minute tumor nodules the size of acini surrounded by connective tissue and for this reason may be mistaken grossly for cirrhosis This is the least common of the three groups Group 1 the large massive nodule is found most frequently in the right lobe of the liver The tumor nodules are pale yellowish gray and stand out against the darker background of the rest of the liver If cirrhosis is advanced it further modifies the gross appearance The tumor tissue does not become pigmented with hemosiderin but becomes colored with bilirubin when jaundice is present However the non neoplastic liver tissue is more deeply stained with bilirubin

Microscopic

The microscopic classification depends on which of the two types of epithelial cell of liver is involved in the tumor formation (the liver cell or the bile duct epithelium) The terms malignant hepatoma or hepatocellular carcinoma and malignant cholangioma or cholangiocellular carcinoma are applied depending on the origin of the tumor When both cell types partake in the tumor formation the term cholangiohepatoma may be applied The term mixed tumor should be avoided because it is used in reference to a specific type of tumor of embryonal origin The hepatocellular carcinomas are by far the commonest three to four times as many hepatoma as cholangiomas are seen

The two cells like the mother cell differ in their appearance and arrangement The hepatoma contains polygonal or polyhedral cells arranged in cords and contains a capillary or endothelial network The tumor cells may be multinucleated and show mitoses Occasionally they undergo fatty degeneration and necrosis The bile duct cell carcinoma is cuboidal or cylindrical and forms tubules or alveoli The lumen of these may contain bile and these tubules or alveoli are surrounded by a network of fibrous tissue The greater abundance of fibrous tissue in this group may help to classify it when the cell type is not distinguishable The cells of the hepatocellular carcinoma may show bile granules within the cell while the cells of the cholangiocellular carcinoma do not

l Esperance has described an atypical primary hepatoma multiple hemorrhagic hepatoma (Ewing) These tumors contain cells arranged in cords surrounded by large vascular channels In some areas these tumors resemble peritheliomas or chorioepithelioma of the liver which is not believed to be a primary tumor of the liver

Metastases

The infrequency of widespread or distant metastases is one of the remarkable features of this tumor The multinodular variety of



Fig Malignant hepatoma of liver (solitary massive tumor type) involving right lobe Patient age No cirrhosis jaundice due to compression of hepatic ducts

primary hepatoma is probably based on intra hepatic spread rather than multicentric origin The tumor invades blood vessels early (hepatic and portal veins) this makes the infrequency of distant spread even more surprising Distant metastases are commoner in the cholangiomas in spite of the fact that these tumors do not invade the blood vessels Perhaps this is due to the fact that the hepatoma consists of highly specialized cells which grow best in the liver Metastatic hepatoma cells continue to secrete bile in their new sites

Wilbur and co workers reported that 26 of their 49 cases showed extrahepatic metastasis In Hoyne and Kernohan s series 55% of the hepatomas and 91% of the cholangiomas showed distant metastases The commonest sites of metastasis are the lungs lymph nodes and mediastinum In Charache s collected series 20% showed pulmonary metastases while in the series of Wilbur and co-workers about 25% showed such metastases Bone metastases were noted in 18 cases in the literature by Charache (or an incidence of 1 6%) 3 cases of the Mayo group and 2 cases of the San Francisco group localized in the spine The vertebral column is the site of predilection when the skeleton is involved Panmyelophthisis from skeletal metastases was recently reported by Auerbach and Trubowitz In addition metastasis occurs in the peritoneum stomach duodenum gallbladder pancreas spleen and adrenal glands The brain is a rarer site of metastasis (one case each reported by Barre and Paillas and by Saward) Metastases to the heart have been reported on several occasions

TABLE 30

Rare Metastatic Sites

Author	Site	No of Cases
Charache (1939)	Skeleton	18 (1 6%)
Hoyne & Kernohan	Skeleton	3
Saward (1942)	Brain	1
Barre & Paillas (1934)	Brain	1
Auerbach & Trubowitz (1950)	Skeleton (Panmyelophthisis)	1
Gregory (1939)	Heart Inferior vena cava Right auricle	1
Culpepper (1934)	Heart Inferior vena cava	1
Sanford (195)	Heart Inferior vena cava	1
Schupbach Jr & Chappell	Adrenal gland	1
	Lumbar spine	1
	adrenal gland	1

and are usually based on extension by way of the hepatic vein and the inferior vena cava. The rare metastatic sites are referred to in Table 30.

Pathology—Summary

Size
- Usually large, average weight 3925 gm

Gross Groups of Malignant Hepatoma
1. Solitary massive tumor (right lobe most common)
2. Multiple nodular tumors
3. Diffuse group ("carcinomatous cirrhosis") (least common)

Microscopic
- Liver cell (malignant hepatoma) (75% to 80%)
  - Polygonal cells arranged in cords
  - Capillary network
- Bile duct cell (malignant cholangioma) (20% to 25%)
  - Cuboidal or cylindrical cell
    - Arranged in tubules or alveoli
  - Abundance of fibrous tissue
- Both cell types (cholangiohepatoma)

Metastasis
- No distant metastasis in 40%
- Pulmonary metastasis in 20% or more
- See table for rare sites

CLINICAL FEATURES

The symptoms of this neoplasm are not diagnostic. A sudden and rapid deterioration of the clinical picture in a pre-existing cirrhosis may give a signal of the presence of carcinoma. While in most cases there is a rapid downhill course, occasionally the presence of a neoplasm or any serious disease is unknown to the patient and the hepatic enlargement is discovered accidentally.

Berman in his series divides the clinical manifestations into five groups: (1) frank carcinoma with symptoms pointing to the liver in 63.6%; (2) acute abdominal catastrophe 9.1%; (3) febrile (cancer) course with fever a salient feature 7.6%; (4) occult carcinoma which is discovered accidentally 15.1%; and (5) metastatic carcinoma with presenting symptoms referable to other organs involved 4.6%. For summary of signs and symptoms see Table 31.

Symptoms

Pain, abdominal in localization, is present in a majority of patients—70% or more. It is usually not severe or cramp-like as is the case in involvement of hollow viscera. It is usually dragging or aching in nature and situated in the right upper abdominal quadrant or epigastrium. The pain may be aggravated by move

TABLE 31

Signs and Symptoms of Primary Carcinoma of the Liver

Percentages according to Series Reported

Sign or Symptom	Hoyne and Kernohan	Eggel	Twil	G ne	Wilbur, Wood and Willett	Berman	S k pha k and Chappell
Jaundice	58.1	61	34.3	5	60.0	80	56
Weakness	87.1	—	88.8	—	—	94 (Weakness and Loss of weight)	—
Loss of weight	71	— —	—	41	5.5		86
Ascites	77.4	58.5	4	66	60.0	7	5
Abdominal pain	87.1	—	8.9	9	72.5	71	93
Abdominal distention	87.1	—	—	—	—	—	—
Nausea	45.2 (Nausea and Vomiting)	—	2.2 (Nausea and Vomiting)	—	—	—	—
Vomiting		—		—	—	44	—
Edema of ankles and/or legs	74.2	41	84.3	15	4.5	40	50
Palpable spleen	19.4	3	38.9	34	—	—	1
Dilated superficial abdominal veins	5.8	—	5.2	—	—	—	29
Fever	58.7	14	7.6	—	—	53	1
Palpable abdominal mass	58.1	—	67.9	—	5	86	93

Expanded from the study by R. M. Hoyne and J. W. Kernohan, Arch. Int. Med., 9: 532, 1947.

ment and occasionally radiates to the back Pain is due to enlargement of the organ stretching of Glisson s capsule and involvement of the peritoneum When the peritoneum is involved the pain may be severe and is a sign of advanced disease Sudden onset of severe abdominal pain and signs of peritonitis may be due to perforation of a necrotic tumor and account for the acute abdomen of Berman

Dyspepsia of varying degree is frequently present This may consist of anorexia bloating eructations and upper abdominal discomfort Nausea and vomiting may be present and all these symptoms may be aggravated by intake of food It should be pointed out that these are symptoms frequently seen in uncomplicated cirrhosis and in a patient already having this disease they would not arouse any suspicion of a serious complication

Loss of weight and asthenia may be rapidly progressive and are seen in over 50% of cases

Bleeding may be a prominent symptom and may be serious enough to cause death Epistaxis is occasionally present and may be severe Bleeding from esophageal varices may result in marked hematemesis and exsanguinating hemorrhage Intra abdominal bleeding of slight degree is frequent and is revealed by bloody ascites Sudden and fatal intra abdominal hemorrhage may occur owing to erosion of a large vessel by the neoplasm Tarry stools or occult blood in stools may also occur but not nearly so commonly as in neoplasms of the hollow viscera In 24% of Wilbur s cases hemorrhage was a responsible factor for death of the patient

Dyspnea may be present because of ascites or because of the anemia and general debility However massive pulmonary metastasis has been reported as a cause The pulmonary symptoms in such cases may mask the true nature of the disease Dyspnea may also be present because of involvement of the vena cava and heart by metastases

Physical Findings

Hepatic enlargement This is the most constant physical finding and is seen in about 80% of cases In addition to the size gross nodularity is frequently detected The finding of a large solitary node in a patient with pre existing cirrhosis should suggest the diagnosis A rapidly enlarging solitary mass in the liver even in the absence of cirrhosis should arouse suspicion of this disease The mass is hard and may be tender when hemorrhage and necrosis have developed If the neoplasm is in the dome of the right lobe the right side of the diaphragm may be elevated In massive involvement of the left lobe, the mass is on the left side and may be mistaken for an enlarged spleen This may result in much diagnostic confusion

Ascites A common finding this occurs in 47% to 86% of cases (table 31) This may be marked and may require paracentesis The ascitic fluid may be straw colored bile stained or hemorrhagic The ascites frequently may be due to one or a combination of the following factors (1) pre existing cirrhosis (2) thrombosis of the portal vein and (3) spread of the carcinoma to the peritoneum The last is the least likely cause The character of the fluid depends on the pathogenesis of the ascites Wilbur Wood and Willett failed to find neoplastic cells in the ascitic fluid of their patients

Edema This condition in the legs may be due to hypoproteinemia pressure on or direct involvement of the inferior vena cava or a combination of these factors It has been observed in as high as 84% of some series of cases

Dilatation of superficial abdominal veins is a prominent finding and may be due to the pre existing portal hypertension or to secondary involvement of veins

Protrusion of the umbilicus takes place because of the increased intra abdominal pressure Spider nevi are seen in patients with pre existing cirrhosis

Jaundice It is common to find jaundice of variable degrees It may be seen in as high as 80% of cases Berman calls it a late s gn but in a disease that may run its entire clinical course from diagnosis to death in several months any sign is a late one Icterus is usually mild to moderate but Hoyne and Kernohan reported one case in which the serum bilirubin was 21 7 mg % Berman found an icteric index of 7 to 60 and Wilbur et al an index of 10 to 176 units I have seen a patient with

primary carcinoma of the liver who was intensely jaundiced

Fever Berman reported temperatures up to 103 F (39.4 C) in 40% of his cases others have reported a smaller incidence of fever The fever is irregular or shows a septic type of curve The onset of fever in a patient with cirrhosis in the absence of infection warrant suspicion of primary carcinoma *Subnormal* temperatures have also been noted Wilbur et al reported a *rectal temperature* under 95 F (35 C)

Spleen This organ is palpable in 10% to 30% of cases At autopsy *the spleen is much more* frequently enlarged The difficulty *in the* clinical detection of a large spleen depends upon the ascites abdominal distention and a markedly enlarged liver The splenic enlargement is secondary to the cirrhosis or portal vein involvement with tumor

Laboratory Findings

Blood The red blood cell count and hemoglobin are decreased in about one third of cases but as a *rule the anemia* is not so marked nor so frequent as that seen in neoplasms of the hollow abdominal viscera The leukocyte count is usually normal but leukocytosis of moderate degree can occur A leukocyte count of 6 000 has been reported As a rule the platelet count is normal However panmyelophthisis due to bone marrow metastases has been reported with a marked decrease of all blood elements

Urine The urine shows the presence of bilirubin in the icteric patients and increased amounts of urobilinogen may also be present



Fig 3 Metastatic car[illegible] of the l[illegible] primary [illegible] *n pancreas* Liver weighed 4000 gm This male patient age 41 had [illegible] 4½ m[illegible] th[illegible] pres[illegible] epigastric pain rad[illegible] to th[illegible] back 1½ months pro[illegible] [illegible] weight loss [illegible] lbs [illegible] 6 months [illegible] examination [illegible] revealed marked icterus [illegible] 8 cm below c[illegible] margin [illegible] Serum bilirubin [illegible] mgm%. Thymol tur[illegible] C[illegible] cholesterol flocculation neg[illegible] Alkaline phosphatase 9.4 Bod[illegible] T[illegible]tal [illegible] 6.1 gm Albumin 3.[illegible] gm [illegible] 6 gm T[illegible] cholesterol 19[illegible] E[illegible] 68 Stool occult blood pos[illegible]

ment and occasionally radiates to the back Pain is due to enlargement of the organ stretching of Glisson s capsule and involvement of the peritoneum When the peritoneum is involved the pain may be severe and is a sign of advanced disease Sudden onset of severe abdominal pain and signs of peritonitis may be due to perforation of a necrotic tumor and account for the acute abdomen of Berman

Dyspepsia of varying degree is frequently present This may consist of anorexia bloating eructations and upper abdominal discomfort Nausea and vomiting may be present and all these symptoms may be aggravated by intake of food It should be pointed out that these are symptoms frequently seen in uncomplicated cirrhosis and in a patient already having this disease they would not arouse any suspicion of a serious complication

Loss of weight and asthenia may be rapidly progressive and are seen in over 50% of cases

Bleeding may be a prominent symptom and may be serious enough to cause death Epistaxis is occasionally present and may be severe Bleeding from esophageal varices may result in marked hematemesis and exsanguinating hemorrhage Intra abdominal bleeding of slight degree is frequent and is revealed by bloody ascites Sudden and fatal intra abdominal hemorrhage may occur owing to erosion of a large vessel by the neoplasm Tarry stools or occult blood in stools may also occur but not nearly so commonly as in neoplasms of the hollow viscera In 24% of Wilbur s cases *hemorrhage was a responsible factor for death* of the patient

Dyspnea may be present because of ascites or because of the anemia and general debility However massive pulmonary metastasis has been reported as a cause The pulmonary symptoms in such cases may mask the true nature of the disease Dyspnea may also be present because of involvement of the vena cava and heart by metastases

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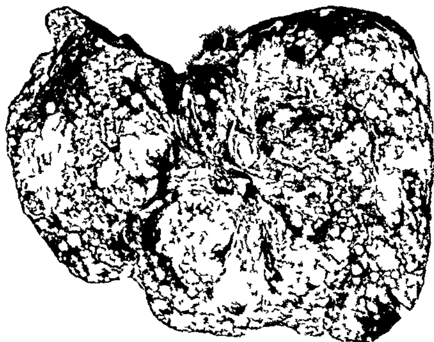


Fig 23 Metast tic c rci m f th l er prim ry i j n r a I i er weighed 4000 gram This male p tient ag 41 had 1a hea tor 4½ m nth p e ire l ke epiga t ic p rad t ng to th back 1½ m nths p o gre e jaund ce i m th w ight lo c lb in 6 m nth Phy cal exami at n re e l d marked icte u l v 8 cm b l w c tal m gin firm nod l r nd l ght l tend r Ser m b l r b 3 6 mgm% Th m l t r b d ts i n t C ph l chol t ol flocc lati neg t e Alk l e phosphat e 9 4 B dan ky un t Tot l pr t n 6 1 gm Alb im gms C l b l 6 gm Tot l chol sterol 19 E t s 68 Stool occ lt blood po it v



Fig 24 Metastatic (?) carcinoma of the liver (X 140) demonstrated by needle biopsy This 3 year old male patient suddenly developed weakness and hepatomegaly Liver function tests were normal with the exception of *BSP 6% retention* and the *alkaline phosphatase* *Comori units* The biopsy established the diagnosis of carcinoma Subsequent autopsy revealed it to be a primary malignant cholangioma

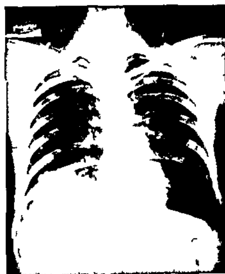


Fig 5 Chest X ray of patient with primary hepatoma of the right lobe of the liver showing irregular elevation of the right diaphragm This led to correct antemortem diagnosis (Photograph of liver fig)

unless there is obstruction of all the hepatic ducts or the common bile duct Albumin is occasionally present

Stools The stools may be tarry or contain occult blood if bleeding into the gastro intestinal tract is present If there is extra hepatic obstruction there is an absence of urobilinogen in the stools The presence of excess *fat in the stools has been reported* Ova and parasites should be looked for especially in Oriental patients in whom ova of Schistosoma or Clonorchis sinensis may be found regardless of the etiologic importance of these

Blood chemistry Urea nitrogen is occasionally elevated Spontaneous *hypoglycemia* has been reported by several workers and this in the absence of pancreatic involvement This is probably dependent upon liver cell destruction and interference with gluconeogenesis

Liver function tests are variable and depend to a great extent on the presence of an underlying cirrhosis If there is marked derangement of the liver profile the presence of cirrhosis is likely Thus the total proteins may be decreased with a preponderance of globulin The serum bilirubin may be increased as noted before The flocculation tests may be positive Two tests are most likely to be positive in both primary and metastatic carcinoma of the liver alkaline phosphatase is likely to be elevated and sulfobromophthalein (Bromsulphalein BSP) is likely to be increased When these tests are strongly positive and the others are negative malignancy in the liver must be suspected (Figs 23 and 24) I would expect the alkaline phosphatase to be higher in malignant hepatoma than in metastatic carcinoma

X ray This test is valuable chiefly in helping to rule out a primary carcinoma of the gastrointestinal tract Schatzki pointed out that the roentgenologist can help to suggest the disease by demonstrating (1) esophageal varices (2) large spleen and small liver (evidence of cirrhosis) (3) a mass in the region of the liver and (4) evidence of metastasis However the localized irregular elevation of the right side of the diaphragm which he mentions is of greatest help when found In one case that I observed antemortem diagnosis was

based on this finding along with the clinical picture (Fig 25) The bulging of the diaphragm due to an abscess is usually smooth and uniform moreover there is complete fixation of the diaphragm which is less likely to occur in carcinoma A left lobe neoplasm distorts the gastric air bubble and displaces the fundus downward and medially

Biopsy In any neoplastic disease this is the most valuable laboratory procedure Peritoneoscopy has offered an opportunity for gross inspection of the organ as well as obtaining a biopsy (Ruddock) With perfection of the technique of needle biopsy of the liver this procedure will probably supersede peritoneoscopy for the diagnosis of liver disease This procedure if successful should establish a diagnosis (Fig 4) however occasionally even this may not be conclusive The cells of a malignant hepatoma may resemble regenerating cells of cirrhosis and a malignant cholangioma may resemble metastatic carcinoma

20

Other Malignant Neoplasms of the Liver Diagnosis, Differential Diagnosis, and Treatment

MALIGNANT neoplasms of the liver arising from mesenchymal tissues are truly medical curiosities Their interest to the clinician is slight not only because of their rarity but because differentiation from carcinoma is virtually impossible *without* histologic evidence and the prognosis and treatment are the same

Sarcomas

Jaffe collected 48 cases of true primary sarcomas of the liver Some doubtful cases were probably neuroblastomas Twenty nine of these sarcomas were found in cirrhotic livers indicating the close association of this neoplasm with cirrhosis Sarcomas are said to be commonest in infancy and old age but the association with cirrhosis would suggest a different age distribution Jaffe also added another case of combined primary carcinoma and sarcoma to the two other cases in the literature In his case there was a massive spindle cell sarcoma in the right lobe and the left lobe showed the presence of malignant hepatoma The liver showed a diffuse cirrhosis Willeford and Steinbridge recently reported a case of primary undifferentiated sarcoma of the liver in a 6 year-old girl who was running a febrile course

The round and spindle cell sarcomas *cannot* be differentiated clinically from carcinoma except by liver biopsy The clinical course is also similar

Hemangioendotheliomas

Hemangioendotheliomas that show malignant tendencies should preferably be referred to as endotheliosarcoma angiosarcoma or malignant hemangioma Stout reported two cases with metastasis to the pancreas kidney adrenal spleen diaphragm and lungs In one case there was metastasis to the heart Histologically these tumors show atypical endothelial cells in greater numbers than are required to line the vessels heaped up in bizarre fashion These form vascular tubes with a delicate framework of reticulum fibers and marked

tendency to anastomosis McMahon and co workers reported a curious case of endothelial cell sarcoma in a woman of 70 who received Thorotrast injections for diagnostic purposes 12 years previously She died of shock from intraperitoneal hemorrhage These vascular sarcomas may be differentiated clinically from *the solid neoplasms by their softer texture* and their marked tendency to severe hemorrhage Liver biopsy in these tumors may result in severe hemorrhage but aspiration with a sharp needle may be attempted and may reveal the vascular nature of these neoplasms

Mixed Embryonal Tumors (Wilms s Tumor)

Mixed embryonal tumors (Wilms s tumor) *of the liver are very rare only 26 cases having* been reported up to 1949 and only two in the United States Sixty seven per cent of these were in children Malignant characteristics were noted in 74% of cases but metastases in only 19% Milman and Grayzel presented an excellent review of the literature and reported a case of their own These tumors are of interest because of their occurrence predominantly in *children and because of the low grade malig* nancy Early exploration and surgical removal may save the life of the patient

Teratomas

Teratomas of the liver are extremely rare Willis denies finding true teratomas in ab dominal viscera outside of gonads Those reported in other situations he believes may *be imperfect twin inclusions* Yarbrough re ported the removal of a teratoma in a 6 week old infant This tumor was attached to the liver and contained every tissue of the body including nerve elements The child was living and well three years later

Diagnosis

Because primary malignancies of the liver are rare metastatic carcinoma should be ruled out before a diagnosis *is arrived at* Therefore a thorough search of the gastro intestinal tract genitalia in the female and the lungs should be made to rule out a primary lesion *When these organs cannot* be implicated the following findings help to confirm the diagnosis (1) evidence of cirrhosis (2) a rapidly enlarging liver preferably with a solitary hard nodule (3) a rapid downhill course with weight loss and asthenia (4) nodular irregularity and elevation of the right side of the diaphragm and (5) *positive needle biopsy of the liver*

Next to metastatic carcinoma the following conditions have to be considered Hepar lobatum gumma of the liver in which the patient shows other stigmata of syphilis as well as a positive serologic reaction The nodules are multiple and rubbery rather than hard and the patient is in a relatively good state Massive nodular hyperplasia from healing hepatitis has to be considered A liver with this condition may present difficulties even at biopsy However *the history of hepa* titis or recent liver necrosis with the liver remaining large the markedly abnormal liver function test especially the flocculation test the tenderness of the liver to percussion and the tendency of the organ to decrease in size may help to establish the diagnosis Benign neoplasms and cysts of the liver which will be discussed presently have to be considered *The slow progression and stationary condition* of these tumors and the relatively good state of the patient will suggest benignancy Cysts may show calcifications which will reveal their identity or eosinophilia if the cyst is parasitic Cysts in general produce few or no symptoms until they are very large Liver abscess must also be considered and differential diagnosis may be very difficult when the neoplasm is accompanied by a febrile course However the fever and leukocytosis are apt to be higher in abscess The liver is extremely tender and the diaphragmatic elevation is smooth The finding of amebae would help to clear the problem *Actually all hepatomegalies have to be con* sidered—hemochromatosis glycogen storage disease amyloidosis and the lipoidoses how ever, these can usually be ruled out without too much difficulty

Diagnosis of Primary Carcinoma

Cirrhosis with rapid deterioration of picture

Rapidly enlarging solitary tumor of the liver

TABLE 3

S mmary of E ght en Cases of Carc noma of the Li er in Wh ch Oper t n on the L ver Was Performed

S Ag	P h l gy	Op ti e F nd g	R	A ho
Mal 13	T mor we ght 2 lb 3 oz Hepat c aden ma	Lob lated tumor occ p ng almo t one half of rt lobe of l er no other organs n ol ed	Excellent he lth 1 yr and 10 mo after operat on work ng	Turner G P oc Roy Soc Med *16* 43 1923
M le 60	Tumor part ally enc p lated L er cell c c noma	T m r z of orange n rt lobe of l ver tho ght to be pr mar carc noma	Well 3 yr fter op rat on	Wr ght G P c Roy Soc Med *16* 56 19 3
Fem l 40	C rc noma	C rc noma of gallbl dder stone mal gn nt nod le of l v r	Well after 15 mo could not b traced later	F ankau C Proc Roy S c Med *16* 59 192
F m le 9	Ad oma of l ve	P toneal cav ty full of bl d pel c o g ns nor mal large cone h ped tumor at interior surface of rt l be of l ver r nt 3 n n tum r from wh ch blood was escap ng first th ught t be ctop c pregn ncy	D ed one ho r after opera t on	Turner P Proc Roy Soc Med *16* 60 9
Femal 57	Ad ma of l er	Preoper t e d agn s s sub cute ppend c t s t mor s ze of cr cket ball n rt lobe of l v r	Pat ent d d well b t d ed f om he t stroke"	K dd F Proc Roy S c Med *16* 61 19 3
F m le 54	C c noma of adr nal re t	Yel ow sh tumo f l ngu l l be of l er	Li ed yr after oper t n	N tch C A R Lancet *1* 334 1923
Female 80		Tumo occup ng almost e t e left l b f l ver m as r g 16 x 1 x 1 cm	Pat nt n good health 17 mo later	Jacks n R H Tr Sc th Surg A *44* 99 1931
Male 35	Pr ma ca c noma of l er	Two t mo s s e of gr pe f u t unde rface of l ft lobe b ped le no other n olvement	Well 11 m l t ga ned 22 lb	Goldb rg S J nd W ll ste n H Rev Ga troenter l *1* 306 1934
M e	Ch l ngi m tum 8½ x 6½ x 4 n 3 lb o	La ge t mor at left lobe f l er	In good health 7 mo after operat on	Abel A L Br t J S rg *1* 684 1934
Mal 4	Encap lated t m r w th ce tr l degenerat on 9 x 8 x 7 cm p mar car c noma	E c p ula d tum r n left lobe of l er ze of ora g embedded ba d of c rhos n w de	D ed 6 m after operat	H ck F S Can d M J 20 169 19 9
Ma 9	Hepa ma utopsy fi d gs metasteas s to rt l b per ton um he rt	Large t m r nvol g left l be n oth f c	D d 6 we ks after oper t n	Lo R J B t J S rg *2* 87 1934
Mal 5	Adenocarc noma of l	Large yst c t mor nvol g left lobe of l ver filled w th bl od cl t and mac erated l ver t s e	P t nt n good heal h 9 mo afte oper n	H t n A B ll t Mem Soc n t ch e *56* 940 1930
M l 4	Pr m r carc oma of l e	Mal gn nt odul t f e b rder of l ver ll othe org n n rmal		Le Cr nd No mand e Med *43* 58 1932
F m le 44	T mor we ght 940 gm ade ocarc m	I ge t m r n ol ng mo t f rt lobe of l e	Al ve 9 yr after per t on	W dell W Ar h f kl n Ch *114* 98 19 0
	Ca c noma of l ft l be of l e b le duct type	L ft l be rem ed		P ckrell K L a d Clay R C Arch Surg *48* 67 1944
F m l 3	S l ary hepat ma	T m n rt lobe f l e	Al 5 y later	Wallace R H Arch S rg *42* 14 1941
	P ma y carc m		R cu r nce 7 yr af e m val	Yeom ns F C J A M A *5* 1741 1909
Femal 3	Mal g ant h p ma	T m r 13 x 10 x 6 cm rt & left l be	Rec rrence 4 y af er m al	S nford C F Ann I t M d *3* 304 932

Ref r ed t b Char he H I m r C rc noma of the L e Am J Surg *43* 96 1939 (Expanded from th t d

Nodular irregularity of the right side of the diaphragm
Positive liver biopsy
High alkaline phosphatase and BSP retention

Differential Diagnosis

1 **From metastatic neoplasms**
2 **From all other hepatic enlargements**
  - **Gumma and Hepar lobatum**
  - **Tuberculosis of the liver**
  - **Benign neoplasms**
  - **Cysts**
  - **Abscess of the liver**
  - **von Gierke s disease**
  - **Lipoidosis**
  - **Amyloidosis**
  - **Hemochromatosis**

Prognosis and Treatment

The prognosis as a rule is quite gloomy in primary carcinoma of the liver The usual life span after the patient comes to the attention of the physician is less than six months Malignant cholangiomas have a poorer prognosis than malignant hepatomas Because of the frequency with which malignant hepatoma is associated with some form of liver damage the prevention of liver damage would reduce the incidence of this most serious of diseases When a tumor develops, surgery is the only therapy that can offer any hope This should be especially true in a malignant lesion that usually does not metastasize widely Surgery apparently has been successful in prolonging the life of some of these patients Yeomans reported a patient who had recurrence seven years after a primary carcinoma of the liver was removed Charache collected 14 instances of surgical removal of primary tumors of the liver, among which were nine cases of carcinoma One of these patients was alive nine years after surgery (see Table 32) Sanford reported one patient who lived for four years after removal of a hepatoma

Wallace (1941) collected 29 cases of surgically treated hepatomas and added one of his own Pickrell and Clay (1944) successfully removed the entire left lobe of the liver in a patient with a malignant cholangioma With improvement in diagnostic procedures and surgical technique the outlook may not be as bleak as in the past

Other malignant tumors of the liver should be extirpated if possible Fox reported the successful removal of a hemangioendothelioma in a child 10 months of age If the tumor happens to be sensitive to radiation such therapy should obviously be used Lymphosarcoma would fall into this category but this is rarely primary in the liver

21 — *Benign Tumors of the Liver*

Benign Hemangioma

Benign hemangiomas (cavernous hemangiomas) are more frequently found in the liver than in any other internal organ In most cases they are small unproductive of symptoms and found incidentally at autopsy or at celiotomy When they reach considerable size they are productive of symptoms and become important clinically Schumacker presented an excellent review Up to 1942 he found 66 cases with surgical treatment and added a case of his own Resection was done in 56 of these Since then successful removal of hemangioma was

reported by Pickrell and Clay (one case) Peale and Coombs (one case) and Altman (one case) This makes a total of 71 cases in which exploration was done and 60 in which resection was done The age incidence was 6 to 76 years with an average of 44 This tumor is commoner among females in a ratio of 4 5 1

Symptoms

The symptoms are usually mild They consist of dyspepsia bloating eructations distention after meals nausea anorexia and vomiting Dysphagia is an occasional complaint These symptoms are probably due to pressure on the stomach or other portions of the gastrointestinal tract The tumor reaches a large size before the patient seeks the attention of a physician In about one half of the cases the patient had noticed the tumor and its presence was one of the presenting complaints This awareness of the tumor by the patient may be present for months or years and in one case it was present for 30 years before professional advice was sought

The tumor may remain completely asymptomatic and is discovered on routine examination Occasionally spontaneous rupture may produce dramatic symptoms of an acute abdominal catastrophe or of shock from internal hemorrhage This of course would require prompt surgical intervention

Physical Findings

The physical findings consist of a tumor which is continuous with the liver frequently to the left of the midline or at the xiphoid less frequently on the right side Auscultation over the tumor may help to establish the diagnosis by the detection of a bruit The compressibility of the tumor may give a hint about its structure The size of the tumor varies but the symptomatic ones are usually rather large The collapsed weight of the hemangiomas reported by Shumacker was 58 to 2500 gm with an average of 900 gm

Needle biopsy of this type of tumor is contraindicated because of the danger of hemorrhage Since most of these occur in the midline or left lobe of the liver the position itself would contraindicate punch biopsy However aspiration with a fine needle may suggest the diagnosis by yielding blood

X ray examination shows most commonly displacement of the stomach to the left or downward or pressure against the lesser curvature On one occasion pressure against the lower esophagus suggested carcinoma of that organ Pressure against the colon has been noted

Other laboratory findings are not contributory Liver function tests are normal Anemia may be present if the tumor is bleeding

Adenomas

Classification

This benign tumor of the liver may be divided into benign hepatoma benign cholangioma and cholangiohepatoma according to the cellular origin Tumors showing both cell elements are sometimes referred to as hamartomas

The cholangiomas are divided into the solid or tubular type and the cystic type (cystadenoma) It is interesting to note that practically all the benign tumors have their malignant counterparts This is important from the point of view of nomenclature and our conception of pathogenesis In regard to the former it is imperative that we modify the terms hepatoma and cholangioma into malignant and benign In regard to the latter one must be wary of possible transitions from one to the other The benign adenomas are encapsulated and show no invasive tendency and do not metastasize or multiply

Incidence

These tumors are not so rare as commonly believed The cholangiomas are commoner than the hepatomas and the cystic type is commoner than the solid type The cystadenoma merges into the next group of hepatic tumors that is true cysts The greater frequency of cystadenomas in the literature may be due to the erroneous inclusion in this group of other types of cysts Warvi refers to 168 or more of benign hepatomas in the literature and he reports seven additional cases Franklin and Downing (1947) reported a pedunculated benign hepatoma in a 23 year-old sailor

Levenson and Mason (1952) reported a hamar toma in a 15 months old infant

Symptoms and Pathology

These tumors remain asymptomatic until they reach considerable size or because of their location produce pressure on important structures They may be discovered on routine examination If the tumor is palpated biopsy by means of a needle or peri toneoscopy may afford tissue for histologic examina tion With small specimens of tissue the differentia tion between the benign and the malignant varieties may not be possible in the borderline cases The hepatomas are composed of liver cell cords arranged in orderly fashion The cytoplasm is eosinophilic and granular and the medium sized central nucleus is not hyperchromic Mitotic figures are rare Portal triads and bile ducts were absent in Warvi s case Hoffman s case showed changes in the tumor indica tive of cirrhosis The cholangiomas are composed of bile ducts lined by single layers of cuboidal epi thelium separated by fibrous tissue Tumors com posed of both elements (benign hamartoma chol angiohepatoma) may resemble cirrhosis

Cysts of the Liver (Nonparasitic)

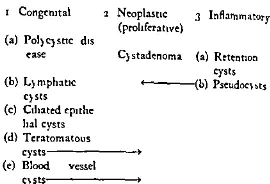
Classification

Cysts of the liver are subdivided into para sitic and nonparasitic The latter group will be discussed in this section while the former will be discussed under parasitic diseases of the liver Bristowe is credited with the first description of nonparasitic cystic disease of the liver in 1856

Jones divides nonparasitic cysts of the liver into the following seven subgroups

1 Teratomatous or embryomatous cysts
2 Pseudocysts
3 Lymphatic cysts
4 Cystic degeneration of liver and kidneys (polycystic disease)
5 Cysts arising from blood vessels
6 *Cystadenoma*
7 Ciliated epithelial cysts
8 Retention cysts

A classification along the line of pathogenesis would be more useful to the clinician and the pathologist but unfortunately the origin of many of these cysts is not clearly established There is an overlapping between congenital and neoplastic factors since a congenital rest may give rise to a neoplasm From a patho genetic point of view the nonparasitic cysts can be classified as follows



1 Congenital	2 Neoplastic (proliferative)	3 Inflammatory
(a) Polycystic dis ease	Cystadenoma	(a) Retention cysts
(b) Lymphatic cysts	←	(b) Pseudocysts
(c) Ciliated epithe lial cysts		
(d) Teratomatous cysts →		
(e) Blood vessel cysts →		

Incidence

When mention is made in the literature of nonparasitic cysts reference is usually to the congenital polycystic disease or retention cysts These two are difficult to differentiate even histologically and therefore the all inclusive term is used These two groups are the com monest and most important of all hepatic cysts The following incidence has been reported 10 cases in 6141 autopsies (0 16%) by Ackman and Rhea and 39 cases (0 19%) in 20 000 autopsies by Eliason and Smith One cannot be entirely certain that some cystadenomas are not included in these statistics Twenty fo r cases of polycystic disease of the liver have been recently reported by Comfort and as sociates (1952)

Pathogenesis and Pathology

The teratomatous cysts the blood vessel cysts the ciliated epithelial cysts the lymphatic cysts and the pseudocysts are extremely rare and of little clinical interest They can be easily differentiated from one another histologically Some of these should properly not be classified as cysts but are actually solid neoplasms with cystic degeneration The pseudocysts fall into this category They consist of neoplasms that undergo necrosis or inflam mation with softening of the central portion Teratom atous or dermoid cysts are embryonic tissue neo plasms with a preponderance of cystic changes Blood vessel cysts may also originate from a developmental defect in intrahepatic vessels but the differentiation from a hemangioma is neither simple nor profitable Again congenital defects and neo plasms merge into each other Ciliated epithelial cysts are lined by ciliated epithelium are usually extremely small (walnut sized or smaller) are of no clinical significance and are probably mucous

retention cysts They are thought to be due to an unknown embryonal defect The lymphatic cysts are due to dilated lymphatic channels and are probably due to developmental defect of these structures They are lined by endothelium and are rather small

The retention cysts are caused by an obstruction of an intrahepatic bile duct due to edema inflammation cicatrization or calculus and progressive accumulation of secretions and bile Since the obstructive lesion is not always identifiable it may be impossible to rule out a developmental defect in its pathogenesis This group is therefore difficult to separate from the next group of congenital cystic liver diseases Grossly the following features may suggest retention cyst 1 It is more likely to be solitary 2 It sometimes contains bile Neither of these is a sound criterion Eliason and Smith found that of 39 solitary liver cysts 11 were associated with cystic disease elsewhere in the body suggesting a developmental defect The retention cysts may be free of bile Multiple cysts and other developmental aberrations favor the congenital nature of the condition Conversely a solitary cyst without cystic disease elsewhere or other congenital abnormalities favors a diagnosis of retention cyst The solitary (retention) cyst may reach enormous size One recently reported contained 3300 cc of mucoid fluid (Caravati)

Polycystic disease of the liver is usually but not invariably associated with polycystic disease of the kidneys and other structures Polycystic disease of the kidneys was present in only half of the patients reported by Comfort and associates Oppenheimer found polycystic disease of the liver in 28 5% of polycystic renal disease Waterson and Morgan mentioned this association in 19% of cases while Moschcowitz found the liver involved in 12% (10 of 85 cases) Other organs involved by polycystic disease are the pancreas spleen ovaries and lungs The liver cysts may dominate the pathological and clinical picture however usually the reverse is true The cysts vary in size from a few millimeters to 10 cm or more They show progressive enlargement hence although congenital in origin they may not reach clinical importance till later life While the entire liver may be involved the disease is most frequently confined to the right lobe

Pathogenesis of polycystic disease of the liver is not so clear as that of the kidneys Morris and Tyson made tridimensional reconstructions of the liver in their two cases of this disease in the newborn The disease was confined to the intrahepatic ducts The lesions in the ducts consisted of distortion segmentation and dilatation Many of the isolated and distorted duct segments were in direct line with branches of biliary ducts This suggests that these segments were previously in continuity with bile ducts but became separated The authors concluded that the lesion in the liver as well as the kidney consisted of degenerative changes and abnormal extension of the process of resorption which occurs normally in first generation of bile ducts

Histologically the cyst walls consist of an outer layer of fibrous tissue of varying thickness The inner surface of the cyst is lined by nonciliated epithelium which varies in type according to the size of the cyst If the cyst is small the epithelium is columnar In medium to large sized cysts the epithelium is flattened into cuboidal and low cuboidal type When the cyst becomes very large the epithelial lining may be absent in spots and the entire wall then consists of fibrous tissue These changes are no doubt dependent on the hydrostatic pressure developed within the cyst producing epithelial flattening The adjacent hepatic tissue shows pressure atrophy and distortion of architecture When the cysts are numerous there is compensatory regeneration of liver tissue This may account for the rarity of signs and symptoms of hepatic failure

The contents of the cysts vary according to the type size and complications In polycystic disease (congenital) the fluid is clear and free from bile The analysis of such a cyst was reported by Monroe and is summarized as follows

Specific gravity	1 010
Nonprotein nitrogen	13 mg %
Cholesterol	trace
Bile	absent
Urobilin gen	absent
Hemoglobin	absent
Total protein	1 5 gm %

In retention cysts the fluid may be bile stained This characteristic as has been mentioned is useful in differentiation of retention from congenital cysts These cysts are subject to hemorrhage and infection Hemorrhage results in a brown or reddish color of cyst contents which gives a strongly positive test for hemoglobin Infection of the cyst gives its contents purulent characteristics These two complications modify markedly the clinical aspects of this disease

Clinical Aspects

Webster refers to 400 reported cases of polycystic disease of the liver the majority of them in children However it has been seen in the entire span of life from fetus to old age The oldest patient was 81

Symptoms are absent if the cysts are small In widespread polycystic disease the clinical picture may be focused on the other organs involved In larger cysts the commonest symptoms are those referable to pressure on adjacent organs especially the stomach duodenum and colon These consist of distention after meals

anorexia eructations nausea vomiting dull epigastric or right upper abdominal quadrant pain Some of these symptoms may become exaggerated in a given case Thus *vomiting may become intractable* Pain may become *excruciating and may resemble that of an* acute abdomen This can occur because of *sudden hemorrhage into the cyst* Pain has been noted to decrease in the recumbent position, *by removal of the pull exerted by gravity* The patient may run a febrile course with chills fever and severe pain over the involved area While jaundice is uncommon it does occur and is due to obstruction of the hepatic or common duct by the large cyst Caravati and co workers and Webster have recently added two cases to the 11 in the literature (McCaughan and Rassieur)

The *physical findings* consist chiefly of hepatic enlargement confined to or predominantly of the right lobe or a solitary rounded mass continuous with the liver The liver may be enormously enlarged and fill the entire abdomen The cystic nature of the mass is rarely discernible because of the marked internal pressure the overlying liver and the *thickness of the cyst wall If the kidneys are* cystic they may be palpated as separate masses

Laboratory Features

The laboratory may be of help in making a diagnosis The x ray may demonstrate a globular mass in the right lobe of the liver that produces pressure on the duodenum and displaces the stomach to the left and the colon downward and to the left This is an important diagnostic point since in renal enlargement the colon is pushed anteriorly and lies over the mass *Other types of neoplasms of the liver* may cause the same colonic displacement as cysts Calcification on x ray has been reported by Finn and McCombs but it is not certain whether this was due to hepatic or to renal calcification Demonstration of polycystic disease of the lungs may be of considerable help

Liver function tests as a rule are normal even in diffuse cystic disease The alkaline phosphatase however has been found elevated and there may be some Bromsulphalein retention The serum bilirubin is increased and is bilirub*nuria in the icteric cases* Urea gen values may become high when the *disease of the kidneys is advanced* Ther also be other urinary findings such as p albuminuria and hematuria

Anemia may be present rarely becau hemorrhage into the cyst The white bloo count is usually normal but a leuk count of 76,000 has been reported

Attempted needle biopsy with accid *aspiration of a cyst has suggested the diag* in one case (Caravati) This may be a dang procedure if the cyst happens to l parasitic one

Treatment of Benign Tumors and C

Benign tumors of sufficient size to be pable or to be productive of symptoms sh be treated surgically This should be not only because of the immediate indica but also because of the possibility of m nancy or because the *tumor may r* sufficient size to defy surgical interven The *benign adenomas are usually well* cumscribed and sufficiently small so that *can be easily removed Cystadenomas* become very large and may present probl similar to those of other cysts

Hemangiomas because of their vascular present a more difficult therapeutic prob However with advances in hemostasis t removal *will be accomplished with gre* ease in the future If this tumor is very ex sive its removal may be very hazardous not impossible It should be pointed out t in 1921 Pick recorded 21 operative cases w 17 tumors excised and 15 recoveries M recently successful resections have been ported by Morris and by Peale and Coon Caldwell and Altman removed a mass weigh 1 1 kg

Cysts may no always be obliterated *su*cally because of their multiplicity Howe up to 1931 77 of these were operated on W improvement in surgical technique, th lesions will be attacked with greater succ in the future If the cyst because of its si cannot be resected marsupialization is a sat factory procedure

Summary

Most important varieties
1 Retention cysts
  Caused by
    Cicatrix
    Edema
    Extrinsic pressure
    Calculus
  Characteristics
    Solitary
    May contain bile
2 Congenital cysts
  Caused by
    Developmental anomaly
  Characteristics
    Multiple
    Cystic disease elsewhere
    Other congenital defects
    Absence of bile

Histology
  Fibrous tissues
  Lined by low columnar or cuboidal epithelium
Complications
  Hemorrhage
  Infection
  Rupture
Symptoms
  Due to pressure on adjacent structures
  Jaundice—due to pressure on extra hepatic bile ducts occasionally
X ray
  Colon displaced downward
  Stomach displaced laterally
Treatment
  1 Excision
  2 Marsupialization

V The Response of the Liver to Chemical Toxins (Toxic Hepatitis)

22 — *General Aspects, Pathology, and Pathogenesis of Toxic Hepatitis*

General Aspects

The vulnerability of the liver to various chemical substances is an old and well-established fact Toxic hepatitis was a problem with British munitions workers in World War I (Stewart 1916) In addition to acute toxicity the chronic effect of poisons on the liver and the possible relationship to cirrhosis have intrigued investigators for many years Mallory in 1935 reported on the similarity between chronic phosphorus poisoning in rabbits and guinea pigs and cirrhosis in man Moon in his excellent review of experimental cirrhosis in 1934 pointed to the widespread use of a variety of chemical toxins to produce hepatic injury

This vulnerability of the liver to poisons is not a sign of weakness but rather a result of its important functions It is to be expected that in the process of excretion and conjugation (detoxification) of chemical toxins that gain access into the body the liver should be occasionally damaged The degree of injury depends on the type of toxin its concentration the state of the host and particularly the normality and the nutritional state of the liver

Ottenberg and Spiegel in their comprehensive review in 1943 listed 42 chemical substances known to produce liver injury and admitted that the list is probably incomplete (Table 33) Since then a number of others have been added The list is constantly increasing with the introduction of new chemical substances in industry and pharmacology

The methods and sources of exposure are four fold (1) *industrial* (2) *medicinal* (3) *accidental* and (4) *suicidal* While there is constant and increasing effort on the part of industry and government to prevent exposure of workers to toxic substances complete elimination of this hazard has not been accomplished This failure depends on (1) carelessness on the part of employees or employers, (2) breakdown in prophylactic equipment and (3) introduction of new chemicals whose toxic potentialities have not been thoroughly assayed Liver injury from therapeutic agents may depend on (1) overdosage (2) occasional idiosyncrasy of the patient and (3) improper evaluation of toxic properties of a drug

Ottenberg and Spiegel classify the mechanism by which the various substances produce the deleterious effect on the liver into three groups (1) direct injury to liver cells, ( ) primary hemolysis with secondary liver damage and (3) idiosyncrasy of liver cell to particular substance (Table 33) There is some overlapping of these three mechanisms in specific instances This classification is an attempt to clarify an interesting and complicated problem which is not well understood

Direct injury of hepatic parenchyma is

TABLE 33

Chemic l Ag nts Producing Ja ndice
Arra ged Acco d ng to Type of Exposure and Predom ant Mechanism of Act n

	G p I Dir t H p y to I	G p II H moly	G p III Id sy y Allergy
Ther pe tic (Agents)	Gold Ethe Chl oform Iod form A rtin Tetra odophenol phthalein D nitrophenol G n din compo nds Synthal n Acr flavine Ars ic Carbon tetr chloride	Phenylhydrazine Sulfonam des Incompat ble blood t ans f ions Tr nitr phen l (Pi ric acid) Hem lytic e a	Arsphenam nes Cinch phens Liv r extract B smuth Mercury S lfona n des
Accidental Contact	Amanit toxi Bean p ison Nitrobenzen Carbon tet chl r de Phosph rus Arsenic B r s	Snake poi ns Bean p i n Incompat ble blood tra sfu ns	
Ind str l Haz rds	Tetrachlorethane C rb n tetrachlorid Nitrobenz e Mang nese Carbon disulfid T in trot luol	A in	
Expe iment l (Agents)	Seleni m C pp r Ict ogen pyrr l arsa late	D st lled water T lue d mine	

R Ottenberg and R Sp eg l The Pr nt Stat s of N n-Ob t ctive Jaund e D to Infecti us and Chem cal Agents *Med c* 2 7 1943

produced by such well known hepatotoxic agents as chloroform phosphorus and carbon tetrachloride These are protoplasmic poisons and animals exposed to them invariably show hepatic injury However even with these toxins the liver damage is not always directly proportional to the concentration of the chemical but is modified by the state of the liver and the nutritional condition of the animal

The hemolytic toxins produce hemolysis first and the hepatic damage may be secondary The liver damage may depend only partially on the chemical ubstance for the resultant anemia and increased demand for pigment excretion are likewise important in their deleterious effect on the liver The presence of jaundice under such circumstances cannot be accepted by itself as evidence of hepatocellular damage Other evidence should be demanded before such an agent is labeled hepatotoxic

The term drug idiosyncrasy is a difficult one to define It is not a true allergy for it shows none of the features of an allergic response although anaphylactic reactions to some drugs are seen Hypersusceptibility does not seem to be a good synonym for here one looks for an exaggeration of the normal action of a drug Goodman and Gilman define

TABLE 34

Localization of Pathologic Change in the Liver Produced by Chemical Agents

Parenchymal Necrosis

Centrolobular

- Carbon tetrachloride
- Chloroform
- Chlorinated hydrocarbons
- Gold compound
- Methyl chloride
- Mushroom poisoning
- Propylthiouracil
- Tannic acid
- Trinitrotoluene

Midzonal

- Chlorinated naphthalene

Periportal

- Allyl formate
- Arsenical compounds
- Phosphorus

Intrahepatic Bile Duct *Obstruction*

- Arsphenamines
- Methyl testosterone
- Thiouracil

idiosyncrasy as an abnormal or unusual response to a drug [which] may occur even to very small doses The classic example of drug idiosyncrasy resulting in hepatic damage is the response to cinchophen

PATHOLOGY

The study of the morphology of the liver after chemical injury is interesting in itself but this interest is heightened by an analysis of the similarity or difference between this type of injury and that seen *in other forms of hepatitis* and cirrhosis The basic types of morphological alterations are similar to those seen in other forms of injury namely (1) the degenerative phase in the acute stage necrosis and fatty metamorphosis and ( ) the proliferative phase in the chronic stage parenchymal regeneration and fibrous tissue hyperplasia

The markedly hepatotoxic agents *such as* chloroform phosphorus carbon tetrachloride chlorinated hydrocarbons and allyl formate in lethal doses produce a grossly shrunken liver of acute red or yellow atrophy This is grossly indistinguishable from the acute atrophy of viral hepatitis Microscopically the severe necrosis of the hepatic parenchyma is striking and may involve all hepatic lobules *However not all areas of the* lobule are equally involved thus in carbon tetrachloride chloroform tannic acid chlorinated hydrocarbons and mushroom poisoning the necrosis is centrolobular while in phosphorus and allyl formate poisoning it is periportal *In some instances the necrosis is mid zonal* (Table 34) Fatty infiltration is also a frequent finding in toxic necrosis Necrosis and fatty degeneration are seen in other vital organs such as the kidneys and heart

If exposure to sublethal amounts of poison occurs over a long period of time with a chance of healing in the interval cirrhosis results In the human being in the final stages this cirrhosis may be difficult to distinguish from portal cirrhosis as was pointed out by Karsner Mallory produced cirrhosis in rabbits and guinea pigs by administration of small amounts of phosphorus over a period of five months or more *He described the formation of eosinophilic granules* in the parenchymal cell cytoplasm which eventually fused to form a hyaline reticulum and this along with the fibrosis and regeneration resulted in a picture identical with alcoholic cirrhosis There *are however notable differences between the* necrosis and cirrhosis due to chemical toxins and viral hepatic necrosis and portal cirrhosis (Table 35) Fatty metamorphosis is a common feature of toxic necrosis but is rarely seen in viral hepatitis The necrosis resulting from most of the poisons is zonal rather than massive as in the viral disease Popper and Franklin elaborated on the distinguishing features of these two types of necrosis *They emphasize* the absence of or scantiness of mesenchymal reaction the gradual death of the cell the zonal distribution of the lesions the presence of cytoplasmic clumps of coagulated protein and the widening of *perisinusoidal spaces in toxic necrosis* When inflammatory cells are present they may be predominately polymorphonuclear leukocytes which show little phagocytosis The slow death of the cell was

TABLE 35

Histologic Differences Between Toxic and Viral Hepatitis

	Fatty Change	[illegible]	*Mesenchymal Reaction*	*Death of Cell*	*Cytoplasmic Clumps of Coagulated Material*	*Widening of Perisinusoidal Spaces*
Toxic	Common	Zonal	Absent or scanty polys if present	Gradual	Present	Present
Viral	Rare or absent	Massive	Marked Lymphocytes Plasma cells	Sudden	Absent	Absent

evident from finding cells in various stages of degeneration The normally basophilic cytoplasm becomes eosinophilic fat droplets appear and clumps of coagulated strongly refractile protein appear around the nucleus These may coalesce and resemble the hyaline bodies described by Mallory in alcoholic cirrhosis

In the chronic and healed stage after repeated sublethal doses of poison one should expect to find a toxic or postnecrotic cirrhosis That is there should be large broad strands of collapsed reticulum structures and large varying sized nodules of hyperplastic regenerating liver cells Actually we find repeated references in the literature both experimental and clinical to portal cirrhosis following carbon tetrachloride phosphorus and arsenic poisoning Franklin and co-workers found on liver biopsy periportal fibrosis extending interlobularly and disarrangement of architecture compatible with portal cirrhosis in a patient who had received Fowler s solution for a prolonged period of time La Due and co workers followed a patient who recovered from phosphorus poisoning with repeated liver biopsies on the 33rd day of illness increased periportal connective tissue was evident The periportal connective tissue was increased on the 86th day so that it joined adjacent portal spaces to form pseudolobulation This resulted in a picture of portal cirrhosis These workers also refer to areas of lymphocytic infiltration contrary to the observations of Popper and Franklin Since the damage from phosphorus is chiefly periportal one should expect the chronic changes in this area

Chronic carbon tetrachloride poisoning has also been observed to produce a final picture resembling portal cirrhosis However this toxin produces centrolobular necrosis Ashburn Endicott and Daft identified the portal and hepatic veins by injection technique and thus demonstrated that in carbon tetrachloride cirrhosis in rats and guinea pigs the connective tissue is primarily related to the central veins When the architecture is markedly disturbed the exact relationships are obscured and portal cirrhosis is mimicked From the clinician s point of view the exact classification of the morphological alterations are only of academic interest since the different types of cirrhosis run a similar clinical course

Effect of Toxins on Liver

PATHOLOGY

1 Acute phase
- **Degenerative changes**
  - **a necrosis**
  - **b fatty metamorphosis**

2 Chronic phase
- **Proliferative changes**
  - **a parenchymal regeneration**
  - **b fibrosis**

ACUTE RED OR YELLOW ATROPHY

(May be difficult to distinguish from fatal viral hepatitis)

1 Produced by lethal exposure to
- **chloroform**
- **carbon tetrachloride**
- **chlorinated hydrocarbons**
- **allyl formate**

2 Sublethal repeated exposures may produce

TOXIC CIRRHOSIS (MAY BE DIFFICULT TO DISTINGUISH FROM PORTAL CIRRHOSIS)

PATHOGENESIS

Vascular Impairment

The exact mechanism by which the deleterious effects on the liver parenchyma are produced by poisons is of inestimable importance since it may throw light on the pathologic physiology of the liver cell in general (Table 36) Rosin and Doljanski *injected allyl formate intraperitoneally into* rats and observed the changes chronologically They noted destruction of sinusoidal capillaries one to two hours after injection of the poison At this time the liver cells showed little or no evidence of injury In three to six hours hydropic degeneration of liver cells was noted but only after 4 hours was marked necrosis observed The lesion was confined to the periphery of the lobule Repeated exposure to this toxin results in cirrhosis

These observations are of extreme importance since with this substance the initial injury is to the vascular structures and the parenchymal cells are injured later and perhaps as a consequence of the circulatory disturbance These workers also observed a similar relationship in experimental urethane poisoning This toxin also damages the capillaries primarily but since this is not as severe as with allyl formate the parenchymal damage is also not so marked These observations revive the question of serous hepatitis as a precursor of portal cirrhosis as proposed by Rossle in 1934 and Popper in 1936

Himsworth proposes that centrolobular necrosis in rats after carbon tetrachloride poisoning may also be due to ischemia The first

TABLE 36

Pathogenesis of Toxic Necrosis

I Interference with vascular supply
  especially in allyl formate and urethane intoxication
    1– hours *destruction of sinusoidal endothelium*
    4 hours necrosis of parenchymal cells
  Possibility of centrolobular compression of sinusoids in other toxins (CCl_4)

II *Interference with enzyme systems*
  A *Alkaline phosphatase disappears in center of lobule*
    55 hours after CCl
      increase peripherally
      centrolobular increase with regeneration
  B *Esterase*—decreases centrolobularly
  C *Pentose nucleic acid*—decreases 5–1 hours after CCl later disappears
  D *Desoxypentose*—decreases
  E *Glycogen* absent 1st day
  F *Succinoxidase* absent 1st day
  G *Cytochrome oxidase*—absent 1st day
  H *Phospho monoesterase* decreases

III Interference with utilization of essential nutrients
  A Trinitrotoluene produces hepatic injury in animals *only* on low protein high fat diet
    1 chemical combines with essential amino acids and makes them unavailable
      fat increases solubility of poison
  B Selenium poisoning creates a deficiency of S containing amino acids
  C Arsenic compound

IV Protective effect of dietary factors against toxic necrosis
  Proteins and carbohydrates protect
  Fats accentuate effects of
    chloroform
    carbon tetrachloride
    arsenicals
  Nucleic acid—protective
  B_{12}—protective

reaction to exposure consists of intrahepatic vasoconstriction followed by marked swelling of the liver cell (Wakim and Mann) This compresses the sinusoids and those farthest removed from the portal blood supply (i e around the central vein) are exposed to the greatest ischemia This hypothesis is further supported by the demonstration that low oxygen tension increases the intensity of the necrosis Comparable results have been demonstrated by *chloroform* intoxication and this form of intoxication is mitigated by oxygen administration Furthermore thyroxin which increases the demand for oxygen increases the severity of hepatic lesions While this theory of the pathogenesis of the hepatic injury from carbon tetrachloride is questioned by observations discussed later it nevertheless focuses our attention on the possibility of producing both acute and chronic liver damage by interfering with its blood supply

Enzyme System Interference

Not all noxious agents work by way of vascular changes and most so called protoplasmic poisons injure the liver cell by direct interference with its enzymatic processes Thus histochemical procedures have been utilized to study early changes in cell chemistry Williams and Greenberg noted a decrease of centrolobular basophilia in three species of experimental animals after exposure to carbon tetrachloride or on a low protein diet They also noted a decrease of ribonucleic acid and positive alkaline phosphatase reaction which was negative in normal cells

Stowell and his group made some interesting observations of the influence of single feedings of carbon tetrachloride on the mouse liver *Alkaline phosphatase* disappears almost completely from the liver the first day after the poison is administered Decrease of this enzyme in the central portion of the lobule is seen within five hours while the cells in the periphery of the lobule contain it in greater abundance On the second day after carbon tetrachloride feeding the alkaline phosphatase reaction gradually increases in the surviving peripheral portion of the lobule The increase of this enzyme at the periphery begins to decline at the end of the sixth day and gradually the central regenerating part of the lobule shows a stronger reaction After 18 days this reaction returns to a normal state *Esterase* another important enzyme shows markedly decreased activity in the centrolobular necrotic area on the second day On the sixth or eighth day the esterase activity is recovered *Pentose nucleic acids* which have an important role in the enzymatic action of cells begin to decrease after five to 12 hours following carbon tetrachloride feeding After 24 hours the pyronine methyl green staining at the center of the lobule has practically completely disappeared At this stage ordinary hema

toxylin and eosin stains do not reveal marked changes This disappearance of pentose nucleic acids is an early sign of cellular damage and precedes the morphological evidence of necrosis The return of the pentose nucleic acid staining reaction is more gradual than the return of alkaline phosphatase Histochemical tests for desoxypentose show that this important substance likewise decreases but does not completely disappear Hepatic *glycogen* is absent on the first day but a strong reaction is noted during the third to fifth day mitotic cells however contain little or no glycogen in their cytoplasm Tsuboi and Stowell later showed decreased amounts of *succinoxidase cytochromic oxidase* and *acid phosphomonoesterase*

These studies in enzyme changes in poisoned liver cell are of tremendous importance inasmuch as they give us an insight into the intracellular chemical disturbance which may be responsible for the morphological alterations These observations further show that the enzymatic changes precede and hence may be responsible for the morphological abnormalities They speak against Himsworth s hypothesis that the cellular damage is secondary to obliteration of blood supply and is chemical for if the cell death were secondary to interference with blood supply and decrease of enzyme were secondary to cell necrosis all enzymes should decrease in proportion to the degree of necrosis This is not the case since the alkaline phosphatase and pentose nucleic acid reduction precede necrosis and are reduced to a greater extent than the other enzymes It appears that these enzymes are specifically altered by carbon tetrachloride While it is true that under the conditions of the e experiments there is an increa e of liver volume owing to water and lipid retention Stowell and Lee found no decrease of sinusoidal space by direct measurements It seems likely therefore that in carbon tetrachloride poisoning the hepatic cell are damaged and destroyed by the subtle di arrangement of cellular chemistry One may envision great and far reaching advances in our understanding of liver disease by unraveling the enzymatic disturbances in different types of liver injury

Deprivation of Essential Nutrient

Thus far we have seen how toxins may produce liver injury by interference with its circulation and its intracellular enzymatic processes another avenue of damage is by deprivation of the liver cells of an essential nutrient Cinchophen and trinitrotoluene produce delayed hepatic necrosis in man Cinchophen does not produce such a lesion in experimental animals nor does trinitrotoluene produce liver injury in normal well fed animals However delayed hepatic necrosis can be produced in animals receiving a low protein high fat diet Himsworth suggests that this diet may facilitate the hepatic necrosis in the following manner The trinitrotoluene increases the metabolic rate of the animal thus creating an increased demand for amino acids which are poorly supplied by the diet This shortage of amino acids is further accentuated by the property of trinitrotoluene to combine with amino acids thus taking them out of the metabolic pool The dietary fat facilitates the development of necrosis by increasing the solubility of the toxin thus facilitating its absorption as well as its concentration in a fatty liver

Another example of the noxiou action of a chemical by dietary deprivation is *selenium necrosis* This has been studied extensively in animals but has never been reported in man If animals are maintained on foods grown on seleniferous soil or if selenium is added to the diet some of them become ill after a period of several weeks The animals that die quickly show evidence of acute hepatic necrosis those that linger on develop a po t necrotic cirrhosis Occasionally the lesions are limited to the left lobe Thu the pathological features of this disease are similar to those produced by a deficiency of the sulfur containing amino acids It is also preventable by supplements of methionine cystine and casein The suggested explanation for this sequence of event is that selenium has replaced sulfur in the amino acids in the plants grown on this type of soil These amino acids are not utilized by the animal and a deficiency of ulfur containing amino acid results

Dietary factors play an important role not only in trinitrotoluene and selenium poisoning but in other toxins as well as indeed in nearly all hepatic diseases Thus it has been shown that dietary factors have a protective action against chloroform carbon tetrachloride and arsenical intoxication Miller and Whipple and Goldschmidt et al showed that carbohydrates but especially proteins have a *protective action* against chloroform hepatic necrosis while fats accentuate the lesion Messinger and Hawkins found the same dietary effects in arsphenamine liver injury Neale and Winter as well as Sundareson found that nucleic acid has a *protective effect against carbon tetrachloride* Von Glahn and Flynn noted that yeast has a *prophylactic effect on lead arsenate cirrhosis* More recently Vitamin B_1 has been shown to have a *favorable effect* on carbon tetrachloride poisoning (Koch Weser et al and Mushett) There is disagreement of the mechanism of action of B_1 along the same lines as in the case of the pathogenesis of carbon tetrachloride liver damage Mushett emphasizes the lipotropic effect of this substance and the preservation of ribonucleic acid while Koch Weser and co workers favor a vasodilating effect as responsible for protection against the poison The favorable effect of proteins is attributable to their probable stimulation of regeneration In any case these experimental observations point to the effectiveness of diet in the prevention and treatment of these intoxications

Mechanism of Hepatic Injury in Hemolytic Poisons

The hepatotoxic action of *hemolytic poisons* may depend on one or a combination of several mechanisms In any hemolytic disease jaundice may be of the acholuric prehepatic type dependent on excess production of bilirubin However the liver is frequently secondarily damaged in these conditions by the chronic anemia and consequent hepatic hypoxia as well as by the increased excretory demand on the liver created by the increased bilirubin production In addition some of these substances apparently have a direct *noxious* action on the liver cell Among the latter should be mentioned *naphthalene phenyl* hydrazine and arsine (hydrogen arsenide) While naphthalene is *primarily a hemolytic* agent the chlorinated naphthalenes (chlorinated hydrocarbons) *have a powerful direct* hepatotoxic action The chief and important *therapeutic property of phenylhydrazine is its* hemolytic action but it probably has an occasional *direct deleterious effect* on the parenchymal cells of the liver Arsine although it has *conspicuous hemolytic* properties by virtue of its arsenical content has direct hepatotoxic action as well It is well to keep in mind that most of the toxins in this as well as the other groups have multiple effects on many organs and their final result is a sum total of their combined actions

23 Industrial (Occupational), Suicidal, and Accidental Hepatic Toxins

Clinical Aspects and Implications

To a clinician a useful classification of hepatotoxins is etiological rather than chemical The two large groups in this category are the *industrial* and *pharmaceutical agents* While the former group is by far the largest the latter may be even of greater interest to the physician because his responsibility here is not only in diagnosis and treatment but also in the

nature of the production of the disease state He must be keenly aware which drugs are potentially hepatotoxic and be on guard to prevent this complication also he must detect it early when it occurs This problem is beset by complexities Pharmaceutical agents (1) are usually only mildly hepatotoxic (2) do not produce this effect in all patients and (3) may not be toxic to animals For this reason the hepatotoxic properties of these agents may remain undetected or under dispute for a long time Because of their relative infrequency the possibility of coincidental hepatitis of independent causation must always be considered In addition in pharmaceutical agents administered by hypodermic injection homologous serum hepatitis must always be kept in mind as a possibility unless the syringes have been properly sterilized (See Section on Viral Hepatitis)

In the case of industrial poisons the above difficulties are not encountered but other problems muddle the picture The mere presence of toxic substance in a certain industrial process is insufficient proof of intoxication The important determination is how much (if any) of that substance is absorbed by the suspected victim Side reactions may detoxify some potentially dangerous chemicals or create new ones Many industrial hepatotoxic agents are also ingested accidentally or with suicidal intent This increases their scope and incidence

PHOSPHORUS

Phosphorus poisoning has been relatively infrequent in the United States since the prohibition of the manufacture and sale of matches made of yellow phosphorus Red phosphorus an allotropic form of phosphorus (used in the manufacture of matches in the United States) is almost innocuous while yellow or white phosphorus is extremely toxic as little as 15 mg may produce symptoms and 60 mg can produce death In China and Japan where yellow phosphorus is still used in the manufacture of matches phosphorus poisoning is on the increase LaDue and coworkers found reports of only nine fatal cases in the medical journals of the United States in two decades but pointed out that the American Museum of Safety listed death of 16 children in 1927 from eating fireworks These workers reported 16 cases with four deaths Rubitsky and Myerson found 14 admissions with acute phosphorus poisoning to Boston City Hospital in a ten year period seven of these patients died In Puerto Rico phosphorus poisoning is common as evidenced by the report of 56 cases seen at San Juan City Hospital in a three and a half year period (Diaz Rivera et al) These intoxications are usually due to ingestion of rat poison roach powder or firework This may be accidental as in children or suicidal as in adults The three papers cited offer a good description of the clinical picture of the acute poisoning as well as a review of the literature

Clinical Features

The symptomatology and the eventual outcome of the poisoning depends on (1) the amount of drug ingested (2) the rapidity and effectiveness of the therapy (3) the modality of the poisoning (accidental or suicidal) and (4) the vehicle in which it was taken If it is taken in a liquid vehicle the mortality rate is much higher especially so if the vehicle is an alcoholic beverage when the mortality is 89% to 100% (Diaz Rivera)

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nature of the production of the disease state He must be keenly aware which drugs are potentially hepatotoxic and be on guard to prevent this complication also he must detect it early when it occurs This problem is beset by complexities Pharmaceutical agents (1) are usually only mildly hepatotoxic ( ) do not produce this effect in all patients and (3) may not be toxic to animals For this reason the hepatotoxic properties of these agents may remain undetected or under dispute for a long time Because of their relative infrequency the possibility of coincidental hepatitis of independent causation must always be considered In addition in pharmaceutical agents administered by hypodermic injection homologous serum hepatitis must always be kept in mind as a possibility unless the syringes have been properly sterilized (See Section on Viral Hepatitis)

In the case of industrial poisons the above difficulties are not encountered but other problems muddle the picture The mere presence of toxic substance in a certain industrial process is insufficient proof of intoxication The important determination is how much (if any) of that substance is absorbed by the suspected victim Side reactions may detoxify some potentially dangerous chemical or create new ones Many industrial hepatotoxic agents are also ingested accidentally or with suicidal intent This increases their scope and incidence

Phosphorus

Phosphorus poisoning has been relatively infrequent in the United States since the prohibition of the manufacture and sale of matches made of yellow phosphorus Red phosphorus an allotropic form of phosphorus (used in the manufacture of matches in the United States) is almost innocuous while yellow or white phosphorus is extremely toxic as little as 15 mg may produce symptoms and 60 mg can produce death In China and Japan where yellow phosphorus is still used in the manufacture of matches phosphorus poisoning is on the increase LaDue and co workers found reports of only nine fatal cases in the medical journals of the United States in two decades but pointed out that the American Museum of Safety listed death of 16 children in 19 7 from eating fireworks These workers reported 16 cases with four deaths Rubitsky and Myerson found 14 admissions with acute phosphorus poisoning to Boston City Hospital in a ten year period seven of these patients died In Puerto Rico phosphorus poisoning is common as evidenced by the report of 56 cases seen at San Juan City Hospital in a three and a half year period (Diaz Rivera et al) These intoxications are usually due to ingestion of rat poison roach powder or fireworks This may be accidental as in children or suicidal as in adults The three papers cited offer a good description of the clinical picture of the acute poisoning as well as a review of the literature

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toxin Increased calcium in the diet seems to have a protective effect against carbon tetrachloride injury while concomitant use of alcohol increases the danger of toxic reactions

The use of carbon tetrachloride as a vermifuge is on the wane and has been superseded by other less toxic agents Its use clinically is to be condemned because of its toxic effects it should never be used in individuals with the slightest suggestion of hepatic damage or who are in a poor nutritional state Strict avoidance of fatty foods decreases its ab orbability

Acute Form

Industrial poi oning can result in an acute or chronic illness Because of its anesthetic properties it may cause drowsiness giddiness and coma in the acute exposure This may be followed by headache nausea vomiting epistaxis ecchymosis convulsions jaundice intestinal hemorrhages and death As in chloroform poisoning the patient may die from acute yellow atrophy of the liver Combined hepatorenal involvement has been described from acute intoxication Such a case was reported from the Mayo Clinic (Pearson 1947) More recently Lartenheimer and Citron emphasized the renal component of this intoxication with the development of a lower nephron syndrome Hepatic necro i and jaundice were present in their patients but the oliguria hematuria anuria and hypertension dominated the clinical picture

Laboratory findings of hepatocellular damage including positive flocculation test decrease of total and esterified cholesterol and increa ed prothrombin time are observed The thymol turbidity test may become positive very early Both hyperglycemia and hypoglycemia are een in the early stages of liver involvement These changes in blood sugar are probably dependent on the lo s of hepatic glycogen and the inability to store it In the chronic tage of poi oning the cells regain their ability to store glycogen and changes in blood sugar are not so prominent

When renal damage is severe blood urea nitrogen and creatinine may reach fantastic heights Electrolyte disturbance with acidosis hypocalcemia and hyperkalemia develop during oliguria During the stage of diuresis hypochloremia and hypokalemia may endanger the patient

Chronic Form

Chronic and prolonged exposure may result in an insidious illness that may be disregarded by the patient for a long time Vague dyspepsia headache or tiredness may be the only symptoms or full blown cirrhosis may suddenly appear Cirrhosis of the liver from chronic expo ure to carbon tetrachloride has been reported by Busch Lyon Poindexter and Greene A case of carbon tetrachloride cirrhosis was also observed by me

Case 3

A 41 year old male patient was employed for 11 years as an assayer of ferrous metal He was expo ed among other things to fumes of carbon tetrachloride About 11 days prior to admission to the hospital he vomited about 500 cc of fresh blood This wa followed by tarry stools and anoth r hematemesis the next day At this time progressive weakness anorexia and progressive enlargement of the abdomen were noted

Physical examination revealed a moderately icteric patient with pectoral alopecia and ascite After paracentesis a firm liver extending about 6 cm below the right costal margin and a palpable spleen were detected

Needle biopsy of the liver showed marked periportal fibrosis

Laboratory finding revealed evidence of marked hepatic involvement serum bilirubin 3 5 mg % serum albumin 1 7 gm % globulin 4 6 gm % thymol turbidity 4 4 units cephalin cholesterol flocculation 3 + and colloidal gold 4 + A barium meal showed esophageal varices

This is an example of cirrhosis from the toxic effects of prolonged expo ure to carbon tetrachlorid However the patient s dietary history re ealed a probable deficiency of proteins This dietary deficiency undoubtedly played a role in the development of cirrhosis by rendering the liver more vulnerable to the action of the toxin This relationship between

Second stage This is introduced if the patient does not die in the first 24 to 48 hours This stage is marked by improvement or disappearance of all symptoms may come on within eight hours after ingestion of poison and may last one to three days This period may give the uninitiated a false sense of security for actually it is the quiet before the storm

Third stage This is ushered in by the toxemia of the absorbed poison and is really the *stage of toxic hepatitis* The gastrointestinal symptoms return Pain however becomes localized to the liver area The liver becomes enlarged and tender and icterus appears 71% of the 56 patients reported from Puerto Rico developed ***hepatomegaly*** which was noted most frequently after 36 hours Patients who develop hepatomegaly after 48 hours have a more favorable prognosis than those that develop it in the first 24 hours Hemorrhages into mucous membranes skin and gastro intestinal tract occur in this stage

Jaundice is not present in all cases (36% of the Puerto Rican group) when present it may be very marked One of the patients reported by La Due and co workers showed complete obstruction to the flow of bile as evidenced by the absence of urobilinogen from the stools and urine This was due to intra hepatic biliary obstruction The usual cause of jaundice is the parenchymatous hepatic necrosis The absence of jaundice is due usually to rapid death before jaundice can develop The lack of this finding does not necessarily preclude severe liver damage for rapid death from hepatectomy and massive necrosis can occur without jaundice

Laboratory Tests

Liver function tests usually do not become abnormal until 48 hours after ingestion of poison Although after that period of time the flocculation tests become positive the prothrombin time increases and brom sulphalein retention may be marked

The interesting fact is that results of other laboratory tests which are not ordinarily considered as liver function tests become highly abnormal and are actually evidence of grave hepatic failure Among these are *severe hypoglycemia* which may be due to the inability of the liver to store and/or break down glycogen While azotemia may be due to concomitant renal damage a relative decrease of urea nitrogen and amino acidemia are signs of hepatic failure of deamination Amino acids especially tyrosine cystine and leucine appear in the urine for the same reason

Hyperphosphatemia of over 8 0 mg % has been observed while the exact cause for this is obscure the obvious explanation may be a discharge into blood of ingested phosphorus

Sequelae

The development of cirrhosis after recovery from a single dose of phosphorus seems unlikely but the biopsy studies of La Due et al appear to show that this is a distinct possibility after ingestion of repeated small doses of phosphorus This eventuality is certainly to be expected

Carbon Tetrachloride

Industrial

The hepatotoxic properties of this substance have resulted in its use in a variety of experimental animals and by numerous investigators for the production of hepatic necrosis and cirrhosis Human poisoning is usually a result of its use as a solvent for gums grease and rubber as paint remover also in metal polishes in lacquers in fire extinguishers in electrical transformers and high tension switches and as a clothes cleaning fluid It is a common constituent of home cleaning fluids

Accidental ingestion may result in intoxication but inhalation is the commonest means of exposure in industry and in the home Therefore proper ventilation minimizes its toxic potentialities

Exposure to concentrations of 100 parts to a million in the inspired air is thought to be without danger however transient symptoms of intoxication have occurred from exposure to lower concentrations On the basis of experiments in animals it is suggested that recovery from exposure to low concentrations may increase the resistance of the individual to the

Benzene Hexachloride

This chlorinated hydrocarbon which is used as an insecticide also has hepatotoxic properties Fitzhugh and co workers have pointed out that the technical benzene hexachloride and its alpha isomer has the same order of toxicity as D D T while its beta isomer is two to three times as toxic and the gamma isomer about one fourth as toxic The effects on the liver consist of hepatic cell enlargement atrophy and necrosis as well as other changes considered specific for some chlorinated hydrocarbons (see below)

Dichlorodiphenyltrichloroethane (D D T)

This powerful insecticide is relatively non toxic to human beings unless administered in very large amounts Harmful effects may result from ingestion and absorption from the alimentary tract or absorption through the skin of solutions of this substance Hepatic necrosis is one of its most serious toxic effects Changes in the morphology of the hepatic cell have been described (Laug et al 1950) which are considered specific for D D T and other chlorinated hydrocarbon group of insecticides These changes consist of enlargement of cell without nuclear enlargement homogeneous acidophilic cytoplasm with basophilic granules in the periphery

Mackerras and West consider numbness weakness headache vomiting and dizziness as early symptoms of D D T intoxication and describe four cases resulting from ingestion of the substance mistakenly used as baking powder Neutrophilic leukocytosis has been mentioned as an early finding in animal poisoning and should be looked for in human beings

Naphthalene

Naphthalene ($C_{10}H_8$) the constituent of moth balls and moth flakes is absorbed through the gastrointestinal tract and can produce poisoning This is especially likely to occur in children as was pointed out by Zueler and Apt They reported four children around two years of age who developed severe hemolytic anemia from ingestion of moth balls This was accompanied by hemoglobinuria hemoglobinemia mild icterus and enlargement of the liver and spleen The clinical picture resembles Lederer s anemia and therefore a history of ingestion of moth balls is important for diagnosis All of these patients recovered with blood transfusions and alkalinization

The hemolytic properties of this substance have been substantiated by experiments on dogs and in vitro It appears that naphthalene causes hemolysis by direct action on the cell membrane

The severity of toxic reactions in different persons from the same dose varies widely The substance is conjugated and detoxified by the liver and then excreted by the kidney The efficiency of the liver in detoxifying it as well as the rapidity of its absorption may be the key to its varying toxicity

In addition to its hemolytic properties naphthalene may also produce focal necrosis of the liver (Konar Roy and De) Therefore the jaundice may be due to increased bilirubin production as well as hepatocellular damage

Chlorinated Naphthalenes (Halowax)

This is a group of chlorinated hydrocarbons in which some of the hydrogen atoms of naphthalene have been replaced by chlorine hence they vary from monochlor to octochlornaphthalene The higher the chlorination the higher the toxicity of these compounds Since they are noninflammable and make good insulators they are used widely as wire insulators and in electrical condensers Workers in these industries are frequently subjected to the toxic effect of these substances Another hazard stems from the fact that they are usually dissolved in carbon tetrachloride

The fumes of these hydrocarbons have a markedly hepatotoxic effect and ventilation must assure that less then 0 5 mg per cubic meter is present in the inspired air Severe and extensive hepatic necrosis has been seen in industrial poisoning as well as animal experiments The human intoxication is accompanied by typical *symptoms of* severe hepatic necrosis anorexia nausea vomiting epigastric pain jaundice disorientation convulsion and coma

diet and hepatotoxic agents established in the laboratory should be looked for in the clinic, and one may be rewarded by finding several causative factors acting synergistically

Trinitrotoluene

Trinitrotoluene (T N T) poisoning occurs in industries manufacturing or handling of this explosive It becomes an important industrial health problem in time of war This was especially true in World War I both in Britain and the United States Palmer and co workers cited the occurrence of 17 000 cases of poisoning with 475 deaths in the United States during World War I In World War II this hazard was markedly decreased by better precautions especially in regard to ventilation since the lungs are the commonest portal of entry

Toxic necrosis of the liver and injury of the bone marrow with anemia and leukopenia results from excessive absorption of this toxin The hepatic necrosis is more severe around the central vein while the peripheral portion of the lobule shows fatty changes Some fibroblastic proliferation and leukocytic infiltration around the portal tracts are described by Stewart

The symptoms are similar to those of other forms of toxic hepatitis The liver is enlarged and tender and the icterus may be intense The mortality was very high in World War I Palmer et al reported three patients who recovered One of these had intense jaundice and marked abnormality of all liver function tests except for normal serum proteins

Tetrachlorethane

Tetrachlorethane ($CHCl_2$—$CHCl_2$) is another substance with toxic properties and is commonly encountered in munition manufacturing Because of its marked toxic properties its use in industry was discontinued after World War I but was resumed in World War II In spite of greater precautions and improved ventilation this volatile solvent was inhaled by some workers in sufficient concentrations to produce signs of toxicity This substance may also enter the body through the gastrointestinal tract and through the skin It has a striking odor resembling carbon tetrachloride While concentrations of 10 parts per million is the maximum safe concentration for prolonged exposure, olfactory detection of the odor requires a concentration of 75 parts per million so that it may produce toxic effects without revealing its presence by the distinct odor

Gurney found that of 277 workers exposed to tetrachlorethane 75 (27 1%) developed nervous and gastrointestinal symptoms Fifty five of the entire group were found to have hepatic enlargement If exposure to toxins is not discontinued this toxic hepatitis may develop into acute yellow atrophy

Hepatic enlargement is an early sign of toxicity and may occur before the subjective symptoms occur It is therefore advisable to determine the size of the liver in the pre employment physical examination and re examine the workers periodically Hepatic enlargement should be accepted as a sign of toxic hepatitis until disaproved The hepatic enlargement may disappear quickly after removal from exposure but the enlargement may remain If the hepatic enlargement persists and the consistency is firm the possibility exists that an irreversible cirrhosis has been produced Clinical jaundice hyper bilirubinemia and urobilinogenuria have been observed in the group with liver enlargement Positive flocculation tests may likewise be an early sign of liver injury

Dichlorethane

Dichlorethane or ethylene dichloride another chlorinated hydrocarbon used as an industrial solvent has toxic properties It is used in a variety of industrial processes Combined with carbon tetrachloride it is used as a roach exterminator Its use as a plastic cement has come into prominence because of its property of dissolving various plastics Lockhead and Close recently reported a case in which the patient died after drinking approximately 30 cc (1 oz) of this substance and cited ten such cases in the world literature Their patient died ten hours after ingestion of the toxin and autopsy revealed diffuse hepatic necrosis

Benzene Hexachloride

Tl chlo nated h drocarb wl cl e l an n ect c de al o l a hepat tox c pr per e I tzhugh and co worker have po nte l o t tl at tl e tecl n cal ben ene hexa ch o de an l t alpl a on er l a tl ame rde t tox c t as D D T vh le t let er t vo to three t mes a tox an l the ga nn a me l out one fo tl a tox c The effect n the l er con st of hepat c cell enlargenent atroph and necr a well a tl e l ange c n lered spec fic tor o ne cl l nate l h dr ocarbons (ee bel w)

D chlorod phe vl rr chl roethane (D D T

Th po erful n ect c de rel at vel n tox c to human be gs unle adn n tered n er large an ount Harn f l effects n ay re ult fro n nge t n an l ab orpt on fro tl e l e ta y tract o ab o pt on tl ough the k n of olut o f th sul tance Hepat c necro s s one of t st ser ous tox c effect Cl ng s n tl e rpho ogy of the hepat c cell have been le l e l (Laug er al 1950) vl ch a e c n dere l pec fic for D D T and other chlo nate l hy lrocarl n gro p of nsect c de Tl e e change on t of enlargen e t of cell w tl ut n clea enlargement h nogeneo s ac loph l c t pla n w th ba ph l granules n the per pher

Macke r an l West le u l ne weakne hea lacl e n t ng an l d z ne ea l n pt t D D T nt x at on an l lever be fou a e re ult g fron nge on t th l tance n taken l t e l a l ak ng powder Neutr ph l c le ko t ha been ment ned a an earl fin l ng n an n al po n ng an l sh l l l e l oked for n h a a l e ng

Na halene

N phthalene (C H) tl e n t tuent of n th l all and n th flakes ab orbed thro gh the ga tro ntest nal tract and can prod ce po on ng Tl s e pec ally l kel t oc a r n ch ldren t was po nted ut l Zueler an l Apt The reported fo r ch ldren ar a n l tw ye ar of age who devel ped evere hemo l t c ane a fr n ngest n of motl l alls

Th s wa accon pa e l by l emoglol nu a hem glob nem a m ld cteru and enlargement of the l ver and spleen The cl n al p ct e e emb e Lederer anem a and the e re a h tory of ge t on of moth ball portant f d agno s All of these pat ent reco ered w tl blood transfu ons an l alkal n at o

Tl e hemol t c propert e t th ub tance ha e b en b tant ated by exper ent on dogs and v tro It appear that naphthalene au es hemoly s l l ect act o n the cell memb ane

The s er ty t tox c react on n d ffe ent per ons fron the sa ne do e ar e w dely The s b tance s conjugated and detox fied by the l ver and then excreted b the k dney The effic ency of tl e l ve n detox f ng t as vell a tl e rap d ty of t al o pt n ma l e the key to t var ng t x c t

In add t on to t l emolyt c pr pert e napl tl alene ma al o prod ce focal necr of the l er (Konar Ro and De) The ef re the jaund ce n ay be due to n rea ed b l rul n pr duct on as well t l ep atocellular dan age

Chlorinated Nap thalenes (Halowax)

Th s a group of chlor nated hy lrocarbons n wh cl on e of the hy lr gen at ms of naphthalene have been repla ed by chlor ne hence they vary fron on chlor to octo chl rnaphthalene The h gher the chlor nat on the h gher the tox ty of the e comp und S nce they re non nfl n able an l n ake good nsulator they are u e l w del a w re in ulators and n electr cal conden er W rker n these nd tr es are frequentl s bje te l to the t x c effect of the e s bstances Another hazar l stems from the fact tl at they are u uall d ol ed n carbon tetrachlor de

The f mes of these hyd ocarbon ha e a n arke lly hepatotox c effect and vent lat on mu t as re that les then o 5 n g per cul c meter p e ent in tl e n p re l a r Severe and exten ve hepat necros ha l een een n in lu tr al po on ng as well as an nal exper n ents The human ntox cat n accompan ed by typ cal s n pt ms of evere hepat c necr s ano ex a na e a vom t ng ep astr pa n jaund ce d entat on convul ns an l coma

The liver is first enlarged and tender and later shrinks. Ascites may develop. Hypoglycemia may be present in addition to other signs of hepatic failure.

The livers of these patients are frequently shrunken to half the normal size. The necrosis may be so widespread as to leave nothing but stroma and bile ducts. However, if the necrosis is not diffuse, it may be chiefly mid-zonal (Strauss).

Methyl Chloride (CH_3Cl)

The toxic properties of methyl chloride are well established. Its use in refrigerators has resulted in many instances of poisoning from its accidental inhalation. Jaundice frequently follows the initial symptoms of drowsiness, apathy, and cramping abdominal pains. Renal injury is indicated by albumin and casts in the urine, terminating in anuria. Fatty degeneration and congestion of the liver are frequently seen at autopsy. In animal experiments, Dunn and Smith have demonstrated fatty changes and centrilobular coagulation necrosis of the liver, hemoglobinuria, and renal damage. Wood reported the case of a 45 year old engineer who developed cirrhosis with ascites after ten years of occupational exposure to methyl chloride fumes. He died from hematemesis from a gastric ulcer.

Toluenediamine

This substance produces a hemolytic anemia in cats and dogs. In the latter species jaundice is more marked, but anemia precedes the jaundice. There is controversy as to the role of parenchymal damage in production of jaundice.

Chromium

Contact with chromium occurs in electroplating, aircraft and shipbuilding industries. Most frequently intoxication with this metal results in cutaneous, gastrointestinal and renal injury. Pascale and associates recently reported the occurrence of toxic hepatitis in workers exposed to chromium in electroplating. Increased urinary excretion of chromium was present. Liver function tests were abnormal and liver biopsy showed focal necrosis.

Lead

Lead poisoning may produce among its pathological changes fatty degeneration of the liver. Wachstein pointed out that lead, like bismuth, may produce nuclear eosinophilic inclusion bodies in hepatic and renal cells. Such inclusion bodies were previously erroneously thought to be caused only by viral infections. If it is kept in mind that metallic poisons may cause these inclusion bodies, an obscure cause of death may be occasionally clarified.

Manganese

The use of manganese in the metallurgical industries results in inhalation of the metallic dust and occasional toxic symptoms. These consist chiefly of neurologic changes pointing to involvement of the basal ganglia of the brain. Occasionally cirrhosis accompanies the central nervous system lesion. This selective attack on specific brain nuclei and liver can also be reproduced experimentally, and is of special interest because of its similarity to hepatolenticular degeneration (Wilson's disease). The problem of manganese poisoning is thoroughly discussed by Von Oettinger.

Favism (Bean Poison)

This unique and ancient disease is caused by the fava bean, also referred to as the horse bean or broad bean. The attacks can occur either from ingestion of the bean or inhalation of material originating in the flower of the plant. This condition is most common in Sardinia and less common in Sicily, Continental Italy, the Greek Islands and North Africa. Only a few cases have been reported in the United States; however, since the fava bean is cultivated in New York, New Jersey, Illinois and California, more cases may eventually be recognized.

Theories of Pathogenesis

There are three theories in regard to the pathogenesis of this disease: (1) the parasitic theory, (2) the toxic theory, and (3) the allergic theory. The parasitic theory, which attributes the disease to a bacterium or fungus, has been all but discarded. While the toxic theory is the oldest, it is still being advocated. It

presupposes a poisonous substance in the seed and flower of this plant which produces the clinical and pathological manifestations in susceptible individuals The word susceptible is the crux of the theories of pathogenesis It does not occur in all persons exposed to the bean and occasionally serious disease results from exposure to minute quantities of material The allergic theory is therefore the most acceptable one but rather than true allergy it may be idiosyncrasy similar to the reaction to cinchophen However sensitization of rabbits to the fava bean extracts and the later production of a syndrome similar to the one seen clinically suggest a true allergic factor

Clinical Features

Jaundice and hemoglobinuria are the two most characteristic features of this form of poisoning A fever of remittent or intermittent character is observed and hepatosplenomegaly develops A typical attack lasts two to six days Death is most common in children and may occur in 8% of cases When death occurs it usually occurs on the second or third day of illness

Hemolysis is the principal effect of the poison hence the jaundice is primarily of the prehepatic acholuric type due to excessive bilirubin production Urinary and stool urobilinogen is increased However hepatic injury occurs either directly from the poison or secondarily from the anoxia and increased burden on the liver or from a combination of these factors

Amanita Toxin (Mushroom Poisoning)

Mushroom poisoning is most commonly caused by the species Amanita phalloides It is infrequent in the United States but common in Europe especially in France The active poison is a thermostable alkaloid amanita toxin Symptoms usually occur five to 20 hours after ingestion of the mushrooms and consist of vomiting diarrhea severe cramping and abdominal pain followed by anuria jaundice muscular cramps and twitching loss of motor control and disturbances of vision Hypoglycemia is common along with other signs of hepatic degeneration The mortality is extremely high—31% to 46% Pathologically extensive fatty changes are seen in the liver as well as the myocardium and kidneys and hemorrhagic diathesis is present The fat content of the liver may be 50% to 80% of the weight of the organ Extensive necrosis of hepatic parenchymal cells sparing only the periphery of the lobule is seen If the patient survives complete restitution of the liver to normal may occur or postnecrotic cirrhosis may develop

24 — *Pharmacological Hepatotoxic Agents*

Arsenic and Arsenicals

Arsenic in the metallic state is nontoxic however its compounds are very poisonous The inorganic compounds are much more poisonous than the organic and trivalent arsenic compounds are more poisonous than pentavalent compounds Arsenicals may cause poisoning from (1) industrial (2) accidental (3) homicidal (4) suicidal as well as from (5) pharmaceutic use It will be more convenient to discuss all these forms of poisoning in this section

Industrial exposure may occur during manufacturing or during the final use of products

carbaminobenzene arsonic acid) is the least toxic of this group while acetarsone is the most toxic Nevertheless it is best to avoid the use of arsenicals in the treatment of amebiasis when hepatic injury is present or suspected

Bismuth

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All the other reports of bismuth hepatitis are open to the same objection Any drug administered by syringe and needle may produce this type of hepatitis unless the instruments are boiled or autoclaved until *the last decade this technique was not usually* adhered to The various authors who refer to bismuth hepatitis or jaundice admit that clinically this entity is indistinguishable from catarrhal jaundice The increased incidence during certain periods may be attributed to a *rise of incidence of hepatitis among the* general population and its ready transmission to these patients by the syringe The incubation period is compatible with a diagnosis of homologous serum hepatitis since most of the reported cases occurred after the last bismuth *injection* which means at least two *months* after the first injection Likewise the three month period after arsphenamine injection does not preclude the administration of the virus during the arsenical infection

The toxic effects of soluble bismuth compounds administered intravenously *in animals* with production of liver injury does not prove that clinical bismuth therapy is hepatotoxic The dosage was much larger in animals and it was given by a different route thus increasing its toxicity

Barnett reported death *in three infants after* administration of a bismuth salt of heptadienecarboxylic acid as suppositories Autopsy showed fatty liver and necrosis in one as well as renal and pulmonary changes and cerebral edema Death was probably not *due to liver injury The toxic effect* of this drug has been ascribed not to the bismuth but rather to the dienecarboxylic acid or a contaminant I am forced to conclude that there is little incontrovertible evidence that the clinical use of the usual bismuth compounds *results in toxic hepatitis* the more acceptable explanation is that the jaundice reported is due to viral hepatiti

Chloroform

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used frequently as an anaesthetic agent Jaundice and acute yellow atrophy were frequently encountered and the symptoms began ten hours to six days after anesthesia This agent has been used extensively experimentally as a hepatotoxic agent It produces changes similar to but perhaps not as intense as those caused by carbon tetrachloride These changes consist of fatty infiltration central necrosis and a hemorrhagic tendency The hemorrhagic tendency is due to inhibition of the prothrombin producing function of the liver Goldschmidt and co workers pointed out that a liberal supply of oxygen minimizes the hepatotoxic propert es of chloroform while anoxia accentuates it The protective effect of proteins and carbohydrates and the deleterious effect of fats has been noted by several investigators and this no doubt has application in human intoxication

Avertin

Avertin (tribromethanol) has a chemical structure similar to chloroform and therefore might be presumed to have hepatotoxic properties Actually its use as an anesthetic agent results only rarely in liver injury However the drug is detoxified and removed by the liver and it has been shown experimentally that a damaged liver does not perform this task as efficiently as a normal liver In cases of liver damage recovery from the anesthesia may be dangerously prolonged Large doses of avertin in a normal individual and smaller doses in patients with pre existing liver disease may result in liver injury Cases of postanesthetic icterus have been reported Anoxia accompanying the anesthesia was thought by some to account for the liver damage however postanesthetic bromsulfalein retention was seen more frequently after avertin than after ether or nitrous oxide Anoxia is probably more severe with nitrous oxide than with avertin anesthesia

Other Anesthetics

The appraisal of the hepatotoxic propertie of anesthetic agents which are only mildly toxic to the liver is difficult and uncertain Other factors in themselves capable of producing liver injury are operating during surgical procedures and the exact influence of each factor is difficult to assay Among these factors can be mentioned (1) anoxia (2) circulatory disturbances and (3) nutritional factors These may act synergistically with the anesthetic agent in producing liver injury (Chapter 28)

Ether

This anesthetic apparently is capable of producing some hepatic dysfunction and this *may be proportional to the anesthetic time* The functional disturbance becomes normalized very quickly Severe anatomic changes in the liver apparently do not occur from this anesthetic agent and acute atrophy has not been reported French and co-workers made a detailed study of the effects of ether and cyclopropane anesthesia on the apparently normal and abnormal liver They found evidence of postoperative dysfunction as measured by bromsulphalein retention serum bilirubin prothrombin time urine urobilinogen and serum alkaline phosphatase in both groups of patients but the abnormalities were more marked in those having preoperative liver damage The changes were similar with the two anesthetic agents and the inference is that the changes were due to the nonspecific stress of surgery rather than the specific anesthetic agent

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The toxicity of cinchophen and its derivatives is of no current importance for the drug has been abandoned in the treatment of rheumatic disorders both because of its toxicity and because it has been replaced by safer and more effective agents However a discussion of its unique toxic effect on the liver is of interest from a historical point of view and like all history should give us a warning about the future since other therapeutic agents may possess similar dangerous properties

Cinchophen was introduced in 1908 but the first fatal case was reported by Richard Cabot in 1925 It was estimated that as much as 9 000 lb was consumed in the United States in one year during its heyday of popularity Considering its widespread and indiscriminate use it is surprising that Palmer and Woodall collected only 191 cases of cinchophen hepatitis in the American literature up to 1936 of these 88 (46 3%) were fatal It is true that many more probably did not reach the medical literature It is not surprising then that this relative infrequency resulted in doubts from some quarters about the toxicity of these compounds

While their uniqueness is still puzzling the hepatotoxic effects are no longer doubtful and can best be referred to by the unsatisfactory term idiosyncrasy Animal experiments were claimed by some to show no hepatotoxic effect Thus Lehman and Hanzlik (1933) concluded that the toxic effects of cinchophen lack experimental basis They were unable to produce liver damage in white rats and only slight and occasional liver damage in rabbits However other investigators succeeded in producing liver injury in various experimental animals by administering many times the therapeutic dose of the drug Coagulation necrosis and complete disappearance of liver cells in small areas were produced in dogs by oral feedings of 7 times the therapeutic dose (Churchill and Van Wagoner Fisk and Barbour) Others have succeeded in producing lesser degenerative changes with smaller doses In spite of the large doses used in animals fatal liver necro is was not produced

Toxic reactions in patients defy prediction and therefore prove impossible to prevent There is no relationship between do age total amount taken and toxic effects Thus some patients took large doses without untoward results while some died after small doses On the other hand large doses have been taken without incidence for long periods of time only to be followed by sudden death from hepatic necrosis Palmer and Woodall cited a patient who took a total of 459 gm over a three year period and then died after ten days of jaundice while another patient died after only 25 gm taken over a five day period Symptoms of toxicity may appear after a long latent period of weeks or months after stoppage of the drug These features suggest a peculiar idiosyncrasy of the liver rather than a toxic effect dependent on overdosage Moreover the idiosyncrasy can develop in an individual who has previously reacted normally The long latent period is indicative of some damage perhaps to a vital enzymatic proce s which is at first clinically undetectable but is self perpetuating and progressive and finally leads to destruction of the liver and the patient Quick attempted to prove that the reaction of the liver to cinchophen is in the nature of an allergic reaction of the Arthus phenomenon type However many of the features of cinchophen hepatitis especially the prolonged latent period between the last dose and the development of toxic symptoms speak against this theory

The clinical picture is like that of other acute necroses of the liver with marked icterus upper abdominal pain nau ea vomiting eventual cerebral symptom and finally coma and death The liver is usually enlarged at first and tender At autop y the liver usually is small and sometimes markedly shrunken Quick reported an anicteric form of cinchophen hepatitis while Weir and Comfort described cases of toxic cirrhosis in patients who recovered

Anticonvulsant Drugs

Dilantin sodium mesantoin (3 methyl 5 ethylphenylhydantoin) thiantoin (phethenylate sodium)

anesthesia was comparable and probably due to nonspecific stress (French et al)

Barbiturates

These drugs, such as Evipal and Pentothal present a different problem as anesthetic agents While there is no convincing evidence that they produce specific liver injury they are detoxified by the liver, and in the presence of pre existing hepatic insufficiency their anesthetic action may be unduly prolonged For this reason they should be used with caution in smaller doses or not at all in patients with established liver disease

Antimony

Antimony compounds are toxic and their toxic manifestations are similar to arsenic compounds Industrial intoxication is rare and unimportant in the United States The therapeutic use of antimony compounds (tartar emetic Fuadin) as anthelmintics in diseases that involve the liver makes their hepatotoxic properties important Apparently these drugs can occasionally cause toxic hepatitis For this reason their use should be accompanied by careful observation for possible hepatotoxic effect They should be discontinued when such signs and symptoms appear

Acriflavin

This dye was formerly used intravenously in the treatment of gonorrhea Eleven per cent of a group of English soldiers who received this treatment developed hepatic involvement with a clinical picture simulating viral hepatitis There was one case of acute yellow atrophy in this group This compound produces hepatitis in guinea pigs and is probably a protoplasmic poison a property which is responsible for its toxic effect on the human liver

Gold

Compounds containing gold (gold sodium thiosulfate) have been used extensively in the treatment of rheumatoid arthritis in the past Toxic reactions have been seen in as high as 25% of patients treated Although the liver is involved less frequently than other organs toxic hepatitis and acute yellow atrophy have been reported as a result of gold therapy Hartfall and Garland cited 11 cases of jaundice among 400 cases in which gold was used and remarked on the similarity of the condition to catarrhal jaundice ' However, Hartung found jaundice uncommon—only 2 among 800 cases Anderson and Palmer found central hepatic necrosis and fatty degeneration in a fatality from gold therapy There seems to be no correlation between dosage and toxic symptoms Gunter and Ivy found no toxic effect on the dog s liver from large doses of gold salts It seems that hepatitis during gold therapy may be either a sign of an idiosyncrasy or not directly attributable to the therapeutic agent Hepatic abnormalities may be present in such chronic debilitating disease as rheumatoid arthritis regardless of therapy In any parenteral therapy homologous serum (syringe) hepatitis must be considered For the toxic effect of radio active colloidal gold see page 175

Mercury

Compounds of mercury exert their toxic effect chiefly on the kidneys A possible toxic effect on the liver must be kept in mind when mercurial compounds are used therapeutically Such compounds are used chiefly as antisyphilitic and diuretic agents In the treatment of syphilis the concomitant use of arsenicals makes it difficult to accuse the mercurials for the hepatic damage encountered However acute yellow atrophy after mercury injections has been reported in nonsyphilitics The tendency to use mercurial diuretics in the treatment of ascites due to cirrhosis of the liver makes it imperative to ascertain whether these compounds have any hepatotoxic properties Waife and Pratt reported a patient who died after repeated injections of mercurophylline The kidneys showed characteristic changes of mercurial poisoning but the liver showed several hemorrhagic areas with necrosis of hepatic cells and moderate periportal fibrosis Even though the hepatotoxic properties of mercurials may be insignificant compared with their nephrotoxic properties these compounds are best avoided in patients with liver disease

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The toxicity of cinchophen and its derivatives is of no current importance, for the drug has been abandoned in the treatment of rheumatic disorders, both because of its toxicity and because it has been replaced by safer and more effective agents. However, a discussion of its unique toxic effect on the liver is of interest from a historical point of view and, like all history, should give us a warning about the future, since other therapeutic agents may possess similar dangerous properties.

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... jaundice developed These ...
... warning so that the ...
... experiences with cinchophen are no ...

... has been compl ... rded
... because ...
... toxic eff ...
... liver is ...
... such as sk ...
... peripheral ner ...
... among pa ...
... The hepatic ...
... after chlo ...
... Intense jau ...
... due to in ...
... h recovery ...
... tendency to ...

... trophenol causes a rapid los ... the hepatic cells Abnormal ... tests can occur in the absence of ... of liver disease

Diethylstilbestrol

When ... synthetic estrogen was first ... was thought to produce liver ... conclusion was based on the ... development of ... hepatic cell changes which were ... be degenerative in nature ... however proved to be cellula... deposi... cases of jaundice have been ... its use ... but the ... relationship is anything ... clear

Methyl Testosterone

The occurrence of jaundice in patients ... was first reported by Werner ... Werner, ... and Kramer ... published a ... of six such cases ... Considering the widespread use of this drug ... is extremely rare ... cases were reported by ... and one by Wood None of these patients received other hepatotoxic ... blood products or injections However the use of a con... minated needle (during other clinical pr ... as a source of in ... or a spont ... ccurring ...
unlikely ... comple ...
The lack ... ton bet ...
of the d ... the a ... jaun-
dice an ... t ... o ... tion
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iled

globulin does not become elevated, however, a moderate elevation of the alkaline phosphatase is observed, and the cholesterol esters may be slightly depressed.

The histologic picture in the biopsies obtained revealed a stasis of bile within the bile capillaries in the central portion of the lobule without evidence of obstruction in the larger bile ducts. The contiguous hepatic cells showed minor alterations, but most of them remained viable and only an occasional necrotic cell was seen. The absence of inflammatory cells speaks against an intercurrent viral hepatitis. However, a second biopsy from one of the patients did show a few lymphocytic aggregates, slight increase of fat and connective tissue.

There is a difference between the post-testosterone hepatitis and the post-arsphenamine jaundice described by Hanger and Gutman, inasmuch as there is no involvement of the larger bile ducts or portal triads in the testosterone lesion. It has been postulated that a specific type of injury of the hepatic cells occurs which interferes with proper hydration of the bile, with a resultant increase of its viscosity and plugging of the intralobular canaliculi.

Paraaminobenzoic Acid

Paraaminobenzoic acid has been used extensively in the treatment of Rickettsial disease. This member of the B complex was administered to three children with rheumatic fever by Cruickshank and Mitchell. All three patients died and showed enlarged and fatty livers, as well as changes in the myocardium and kidney. These authors are inclined to attribute the changes in the liver to the action of paraaminobenzoic acid. Administration of this substance to rabbits did not produce such marked hepatic change.

Paraaminosalicylic Acid, Tibione (Amithiozone) and Isoniazid

Of the newer agents used for the treatment of tuberculosis, tibione is the one most frequently suspected of hepatotoxic properties. Many of the toxic effects reported were in the foreign literature and were poorly controlled. Since tuberculosis as well as any chronic debilitating disease may induce liver injury, it is difficult to appraise how much of the liver injury is attributable to the drugs used. On the basis of a study of 14 patients with far advanced pulmonary tuberculosis under tibione therapy, Falk and co-workers concluded that progressive hepatic dysfunction occurs in those who had pre-existing liver disease. The bromsulphalein test was the best index of the hepatic abnormality. The anatomic changes consisted of fatty metamorphosis and were reversible upon cessation of therapy.

Yesner and Kunkel found no abnormal changes in the liver of seven patients treated with tibione alone and in combination with streptomycin and paraaminosalicylic acid. McKendrick recently reported a case of toxic hepatitis with recovery in a patient on streptomycin and paraaminosalicylic acid therapy. The patient had a high fever (103 F), an erythematous rash, lymphadenopathy and a large tender liver. Another case of toxic hepatitis from paraaminosalicylic acid is cited from the literature (Cuthbert). One should be on guard for the rare cases of toxic hepatitis from this drug, especially when the patient is treated at home.

Isoniazid in lethal doses has been noted to produce liver damage in animals (Benson et al.). Toxic hepatitis with jaundice was reported in one patient receiving this drug in therapeutic doses (Randolph and Joseph).

Phenylhydrazine

This drug, used in the treatment of polycythemia vera, has predominantly hemolytic properties. The jaundice that it produces is therefore chiefly the hemolytic or prehepatic type. In industry the hydrazines have been noted to produce degenerative changes in the liver and cirrhosis. Phenylhydrazine may likewise produce direct or indirect hepatic injury. In experimental studies with the hydrazines, the animals dying early showed only hemolysis, while those dying later showed severe parenchymatous and vascular degeneration.

Toxic hepatitis as well as other toxic reactions from dilantin sodium and mesantoin have been reported by various investigators (Chaiken et al and Kozol) Thiantoin (phenethylate sodium) has been regarded as producing few toxic reactions and these dealing only with reactions of the skin and *hemopoietic system* Recently *in one issue of* The Journal of the American Medical Association four cases of fatal liver *necrosis* occurring during therapy with thiantoin were reported (Butscher and Gallagher and Pryles et al) Autopsy showed massive necrosis with collapse of reticulum framework and a good deal of round cell infiltration The exudative process would suggest the likelihood of viral hepatitis The authors admit that it is difficult to rule out with certainty viral hepatitis but no *epidemiological factor* favoring such conclusion is elicited

It is plausible that these are true instances of toxic hepatitis produced by this drug There were two adults and two children A woman aged 44 a man aged 39 a boy of 6 and a girl of 15 Fatal viral hepatitis is rare among children and infectious hepatitis is uncommon past 40 The prolonged administration of the drug before the fatal hepatic necrosis took place suggests the experiences with cinchophen One patient received the drug for two *months* Two received it for five months and one for *six months before* jaundice developed These reports may constitute a warning so that the tragic experiences with cinchophen are not repeated

Dinitrophenol

Dinitrophenol has been completely discarded as a therapeutic agent because of the frequency and seriousness of its toxic effects Its potentiality *for injuring the liver is not as great as* that for other organs such as skin hemopoietic system eye and peripheral nerves The liver however is foremost among parenchymatous organs damaged The hepatic damage is similar to that seen after chloroform and trinitrotoluol poisoning Intense jaundice with acholic stools probably due to intrahepatic biliary obstruction with recovery has been reported Because of its tendency to increase metabolism, dinitrophenol causes a *rapid loss* of glycogen from the hepatic cells Abnormal liver function tests can occur in the absence of clinical evidence of liver disease

Diethylstilbestrol

When this synthetic estrogen was first introduced it was thought to produce liver damage This conclusion was based on the *occasional development of gastrointestinal* symptoms and hepatic cell changes which were thought to be degenerative *in nature* These changes however proved to be cellular vacuolization due to increased glycogen deposition Isolated cases of jaundice have been reported during its use (Seligman) but the cause and effect relationship is anything but clear

Methyl Testosterone

The *occurrence of* jaundice *in patients* treated orally with methyl testosterone was first mentioned by Werner in 1947 Werner Hanger and Kritzler (1950) published a thorough study of six such cases including liver biopsy in two Considering the widespread use of this drug this toxic reaction is extremely rare Additional cases were reported by Brick and Kyle and one by Wood None of these patients received other *hepatotoxic drug* blood products or injections However the use *of a contaminated* needle (during other clinical procedures) as a source of infection or a spontaneously occurring hepatitis while unlikely cannot be completely ruled out The lack of correlation between the amount of the drug used and the appearance of jaundice and also the rarity of the complication suggest idiosyncrasy *Against this is the fact* that one retreated patient did not develop jaundice *the second time* Another patient cited by Werner did develop jaundice a second time when the drug was repeated

The clinical and laboratory picture suggests bile duct obstruction rather than hepatocellular damage The liver becomes enlarged but *not* tender Serum bilirubin may reach a very high *level—up to 29 mg % Bilirubinuria* is marked but the stools may be free of bile The flocculation tests are negative the serum

globulin does not become elevated however a moderate elevation of the alkaline phosphatase is observed and the cholesterol esters may be slightly depressed

The histologic picture in the biopsies obtained revealed a stasis of bile within the bile capillaries in the central portion of the lobule without evidence of obstruction in the larger bile ducts The contiguous hepatic cells showed minor alterations but most of them remained viable and only an occasional necrotic cell was seen The absence of inflammatory cells speaks against an intercurrent viral hepatitis However a second biopsy from one of the patients did show a few lymphocytic aggregates slight increase of fat and connective tissue

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Saponins

This largely discarded group of drugs includes sarsaparilla guillaja solanine and senega They are all important hemolytic poisons and produce hemolysis even in vitro Because of their property to lower surface tension they are used in cosmetics and soaps Accidental poisoning may result from this source

Stilbamidine

Stilbamidine one of the diamidines recently introduced as a therapeutic agent against protozoal infections and especially in multiple myoma has hepatotoxic properties It has been demonstrated that 75 mg per kilogram in divided doses injected into rabbits and mice results in fibroblastic hyperplasia and histiocytic infiltration at the periphery of the lobule Sometimes the fibrosis was extensive and the hepatic cells next to the fibrous tissue developed a homogeneous hyaline appearance (Seager and Costelnuovo)

Tannic Acid

The question of the toxicity of tannic acid became clinically important because of its extensive use in the treatment of burns When tannic acid is administered subcutaneously or intravenously to various species of animals hepatic necrosis results The necrosis is predominantly centrolobular When tannic acid is sprayed on burned skin surfaces slow absorption results and appreciable blood levels are attained This absorption is sufficient to produce hepatic injury in animals This sequence of events takes place in the clinical treatment of burns with tannic acid Renal damage also occurs consisting of cloudy swelling and fatty changes in the cells of the convoluted tubules and Henle s loops Administration of tannic acid orally results in its rapid conversion to gallic acid which is relatively nontoxic

Thiouracil Propylthiouracil and Methimazole

The commonest and most serious toxic reactions of thiouracil are those affecting the hemopoietic system Gargill and Lesses reported two patients who developed severe jaundice during administration of thiouracil Both patients had pruritus and showed laboratory evidence of biliary obstruction An exploratory operation was performed in one case the extrahepatic biliary passages were patent, but a biopsy showed normal liver cells and periportal round cell infiltration large bile ducts were empty, while the bile canaliculi contained bile thrombi Holoubek and co workers reported a case of fatal hepatitis associated with thiouracil therapy Laboratory tests indicated complete biliary obstruction yet some evidence of hepatocellular damage was present Autopsy revealed chiefly central but some focal necrosis Livingston and Livingston found evidence of hepatocellular damage from propylthiouracil therapy Colwell and co workers reported the death of a patient from propylthiouracil therapy that resulted in agranulocytosis and toxic hepatitis The patient became icteric and had a 4 + cephalin cholesterol flocculation The liver showed centrolobular necrosis slight fatty changes and mild periportal lymphocytic infiltration One must not disregard completely the hepatotoxic effects of thyrotoxicosis in such cases however since the primary disease is usually under control the toxic reactions are chiefly attributable to idiosyncrasy to the antithyroid drugs

Methimazole one of the newer antithyroid drugs has been noted to produce toxic hepatitis (Rosenbaum and Reveno) The toxic reaction has no bearing to the size of the dose

Thorotrast

The use of Thorotrast for clinical visualization of liver and spleen has been avoided by most clinicians because of its potential toxic properties In animal experiments the radio active properties of the compound have been productive of neoplasms and damage to hemopoietic tissues and liver Yates and Coe in their extensive experience saw no justification for these fears In 286 cases observed over a period of ten years with 68 of the patients surviving over one year no damage attributable to Thorotrast was noted However the recent report of a hepatic endothelio

sarcoma in a patient who received this drug 20 years previously (see section on Neoplasms) again emphasized its potential dangers at least in stimulating hepatic neoplasia

Irradiation

There is little information in regard to the response of the human liver to irradiation In dogs extensive fibrosis of the liver is produced by high doses of unfiltered radiation The clinical use of radioactive colloidal gold which is taken up by phagocytic and reticulo endothelial cells including those in the liver may expose this organ to injury Hahn and his co workers produced marked changes in the liver of dogs by intravenous injection of radio active colloidal gold in much larger doses than used in man The morphological altera tions in the liver consisted of disappearance of endothelium and marked fibrous tissue pro liferation around the central veins and the portal tracts The parenchymal injury seemed to be secondary to the vascular changes

Urethane

The apparent toxic effect of urethane on the sinusoidal endothelium of the liver of experi mental animal with subsequent necrosis has been mentioned previously In the clinical use of the drug three cases of hepatic necrosis have been reported The patient reported by Ohler and associates received a total of 2 59 gm of the drug for the treatment of multiple myeloma The liver of this patient showed evidence of acute centrolobular necrosis endo thelial injury and hemorrhage The vascular changes suggest that the drug was probably the responsible factor in the liver injury Meacham and co workers patient was treated with urethane for one year Injury of the central and portal blood vessels with fragmen tation and necrosis was associated with the hepatic cell necrosis

Synthalin

This drug was introduced over two decades ago in the treatment of diabetes Its hypo glycemic effect proved to be due to its hepato toxic properties It interfered with the de aminizing and glycogenetic properties of the liver and in some instances produced acute yellow atrophy

Alloxan

Alloxan chemically related to uric acid has aroused the interest of investigators because of its selective destruction of the beta cells and the islets of Langerhans and the resultant diabetes However its injurious effect on the liver and its mode of action via attachment to sulfhydryl groups enlarges its scope of interest Bailey and co workers cite evidence that substances containing the sulf hydryl group glutathione and cysteine may prevent alloxan diabetes Since some hepato toxic agents likewise act through attachment to sulfhydryl groups and can be counteracted by sulfur containing amino acids methionine and cysteine it is likely that the effect of alloxan on the liver is accomplished by attachment to this vital —SH group

The initial hyperglycemic effect of alloxan before islet damage occurs is attributed by Houssay and co workers to its direct action on the liver and the later hypoglycemia effect to interference with hepatic gluconeogene is Fatty metamorphosis of the liver has been noted in alloxan poisoning Although these changes are minor the possibility cannot be denied that profound interference in hepatic cell function may occur with relatively minor structural changes

Sulfonamides (Incidence and Type of Toxic Reactions)

The therapeutic use of sulfonamides not infrequently results in toxic reactions The older of these compounds are more prone to produce untoward effects Dowling and Lepper reviewing a large series of cases found toxic reactions in 9 9% of patients receiv ing sulfapyridine in 11 8% of patients receiving sulfathiazole and in 7 7% of patients receiv ing sulfadiazine Watson and Spink estimated that one out of 150 patients receiving sulf anilamide or sulfapyridine develop jaundice This toxic reaction therefore while of im portance is not very common even with the more toxic sulfonamides

Jaundice may be due to hemolysis or to

toxic hepatitis or a combination of the two. That hepatic injury from sulfonamide is an uncommon occurrence is verified by the following observations. Of the 1479 patients reviewed by Dowling and Lepper, no instance of hepatitis was noted. Of 28 deaths in New York City attributed to sulfonamides, none were due to hepatic necrosis (Sutliff et al.). However, in children who had received sulfonamide therapy, Menten and Andersch found 38 instances of focal hepatic necrosis in a series of 299 autopsies. The condition was classified as toxic necrosis in three patients, toxic central necrosis in nine, and serous hepatitis (hepatic edema) with beginning central necrosis in 26. Since all these patients died from severe infections, it is fallacious to attribute all the hepatic changes to the chemotherapeutic agents, but the incidence of hepatic necrosis in an autopsy series before sulfonamide therapy was considerably lower.

In animal experiments, the sulfonamides not only have failed to produce hepatic injury, but have been shown to have a protective effect against carbon tetrachloride and chloroform hepatic injury. Administration of sulfanilamide to animals whose livers were previously damaged by carbon tetrachloride resulted in no further damage, but, on the contrary, appeared to lessen it (Machella and Higgins) (Wilson et al.).

Hemolytic Effects

These effects of the sulfonamides are corroborated by numerous observations. Since these reactions can occur without regard to dosage and have not been produced in animals, and since the drugs are not hemolytic in vitro, they are attributed to idiosyncrasy. Watson and Spink have pointed out that there is an acceleration of hemoglobin metabolism in sulfonamide therapy, evidenced by increased fecal urobilinogen, increased reticulocyte count, and decreased erythrocyte count. Severe hemolytic anemia with marked drop in erythrocytes, hemoglobinuria, marked urobilinogenuria, and jaundice is not an infrequent occurrence. This syndrome begins in the first four days of therapy and may follow the administration of as little as 4 gm. of the drug.

The icterus may be mild, barely discernible clinically, or intense. In the patients with intense jaundice there is hepatomegaly, marked bilirubinuria, a good deal of direct reacting bilirubin in the blood, and evidence of hepatocellular damage. Donald and Wunsch reported a patient in whom toxic hepatitis preceded the development of hemolytic anemia. The toxic reactions began eight days after the beginning of sulfadiazine therapy.

Toxic Hepatitis

A toxic effect and even acute yellow atrophy due to sulfonamide therapy, independent of hemolytic phenomenon, have been described. Hepatitis usually occurs later than hemolytic anemia and after a larger amount of the drug has been taken. It may occur one or two weeks after discontinuance of therapy, and in this respect resembles the toxic hepatitis of cinchophen. The onset is insidious, the symptoms are similar to those of other types of hepatitis, and the liver becomes enlarged and tender. The liver function test shows unmistakable evidence of hepatic injury. Chemotherapy should be promptly discontinued to prevent progression and a fatal outcome.

Some of the cases that begin as simple hepatitis may progress to acute yellow atrophy. Fortunately, this serious toxic effect is extremely rare. Herbut and Scaricaciottoli reported two cases of diffuse hepatic necrosis and cited only four other cases in the literature. One of these patients reported by these authors received a total of 9 gm. of sulfadiazine; the other patient (also a female) received 37 gm. without any ill effects. However, one month later the latter patient again was given sulfadiazine, and after 9 gm. toxic symptoms appeared. This sequence of events suggests sensitization of the liver to the drug. Such apparent sensitization with subsequent diffuse hepatic necrosis has been also reported with sulfanilamide by Roche and Stannus as well as others.

In addition to signs of hepatic injury, these patients exhibit skin lesions, febrile reactions, and renal lesions. Robertson described two unique cases of probable sensitivity to sulfadi-

azine in which hepatitis and interstitial nephritis accompanied by marked plasmocytosis and marked hyperglobulinemia developed One of these patients died from liver failure and the other one from renal failure Serum globulin in three determinations was 9 5, 10 7 and 11 ? gm % The thymol turbidity was strongly positive

Relation to Renal Injury

This relationship between renal and hepatic sulfonamide toxicity is an interesting one Kuzma and Polley point out that the incidence of renal sulfonamide complications is increased in the presence of hepatic injury Thus if pre existent hepatic disease is present or sulfonamide hepatic injury takes place renal lesions are more likely to follow They found that 53% of their cases with renal sulfonamide complications had a background of hepatic disease Thus any type of diffuse hepatic disease would make sulfonamide therapy dangerous not only from the point of view of possible further liver injury but also because of the greater likelihood of renal damage It is also true that in renal damage higher blood levels will be attained because of faulty excretion thus increasing the probability of hepatic damage But since the liver also excretes sulfonamides an insufficiency of this organ may throw a greater burden on the kidneys Kuzma and Polley summarize the hepatorenal relationship in reference to sulfonamide complication as follows (a) Toxic injury to a previously diseased liver (b) hepatic protein sulfonamide metabolism leading to the formation of hapten antigens (c) injury on basis of hypersensitivity reactions (d) formation of relatively insoluble acetyl sulfonamide compounds which lead to mechanical obstruction or irritation resulting in inflammation and (e) impairment of gluconic acid sulfonamide conjugation (soluble) accentuating item (d)

AUREOMYCIN

Clinical Observations

The effect of aureomycin on the liver is of more than usual importance in view of its proposed use in hepatic coma and hepatitis

The hepatotoxic potentialities of aureomycin have been extensively studied by Lepper and co workers Of 89 patients who received aureomycin intravenously in dose up to 90 mg per kilogram of body weight none showed evidence of a deleterious effect on the liver Fourteen patients received aureomycin concomitantly orally and intravenously seven of these developed hepatic enlargement and signs of hepatic dysfunction Clinical jaundice was present in four and an additional patient showed hyperbilirubinemia Two patients had serial sulfobromophthalein thymol turbidity and cephalin cholesterol flocculation tests before and after aureomycin therapy and showed slight but progressive deterioration of liver function

Anatomic Changes

Anatomic alterations in the liver were present in all these patients in whom material was available for histological study These changes consisted of vacuolization and fragmentation of cytoplasm confined chiefly in the central zone of the lobule These changes varied in intensity and in some cases autolysis of cells adjacent to central vein was noted The greasy appearance grossly and the vacuolization are both suggestive of increased fat content Some of these patients had hepatic changes indicative of pre existing disease Lesner and Kunkel also found fatty metamorphosis in three out of four patients treated with aureomycin

Animal Experiments

Similar changes in the livers of mice and dogs were produced experimentally by Lepper et al by parenteral administration of large doses of aureomycin Oral administration of this antibiotic produced similar but less marked changes and larger dosage was required Hepatic injury was likewise produced in the rabbit by aureomycin and terramycin administration (Cutting) It should be emphasized that the dosage was far in excess of that in clinical use

Dosage and Mode of Administration

The hepatic abnormalities appear to depend on dosage as well as route of administration

The dosage employed in the cases cited above was very high Dowling and Lepper point out that of approximately 1300 who received *aureomycin orally* none developed liver dys function attributable to the drug Intravenous doses of less than 2 gm per day to an adult are harmless to the liver If oral administration is used concomitant intravenous administration should not exceed 1 gm per 24 hours Such a dosage schedule is safe for a patient with a normal liver or one only slightly damaged by the concomitant infection One may however wonder whether even this dosage may have some deleterious effect on a severely damaged liver such as is seen in acute yellow atrophy or hepatic coma in precisely the conditions for which the use of aureomycin has been ad vocated I have used aureomycin orally in several cases of severe hepatitis in a daily dose of 2 to 4 gm Some of these patients died but the unfavorable course could not be at tributed to this antibiotic but rather to the severity of the illness

Terramycin and Chloramphenicol

One patient receiving terramycin whose liver was studied microscopically showed no fatty metamorphosis according to Yesner and Kunkel In the experimental studies reported by Lepper and co workers the animals treated with terramycin showed changes similar to those treated with aureomycin but less marked Chloramphenicol had to be ad ministered in doses close to the lethal range before any changes in the liver were observed

Treatment

The treatment of acute and chronic forms of intoxication presents slightly different prob lems but in both situations the treatment resolves itself into three objectives (1) elimi nation of the toxin from the environment and the patient (2) general supportive measures and (3) protection of the liver against further damage

Acute Poisoning

In the cases of acute intoxication the success of treatment and the prognosis are inversely proportional to the amount of poison absorbed Therefore if the poison is ingested early gastric lavage or early vomiting results in less damage The use of various substances to prevent absorption of poison is recommended or the induction of catharsis may be resorted to General supportive measures such as combating shock and de hydration with plasma blood and intravenous fluids should be carried out Support of the circulation in the early stages of intoxication is important Severe hypotension from any cause may reduce or stop glomerular filtration Since renal damage with oliguria and anuria occurs in many cases of acute intoxication fluids should be given cautiously to prevent pulmonary edema The serum electrolytes must be watched carefully and replacement therapy be used during diuresis The hyper kalemia during the stage of anuria may be combated by gastric lavage

Chronic Poisoning

In chronic forms of intoxication the removal of the patient from the environment that brings him in contact with the hepatotoxic agent is of primary importance For this reason an inquiry into occupation and possible contact with hepatotoxic substances as well as a knowledge of these substances is essential in the investigation of any case of hepatitis or jaundice The possibility of the use of a toxic pharmaceutical substance must also be con sidered and all the suspected chemicals must be promptly eliminated It must be emphasized that some patients continued working with chlorinated naphthalenes (halowax) after signs and symptoms of toxic hepatitis appeared This oversight may have cost these patients their lives The recognition and elimination of these toxic substances applies to prophylaxis as well as active therapy Employees must be carefully protected from inhaling ingesting or absorbing these toxins through the skin Timely removal from the noxious environment not only may prevent a fatal outcome but may prevent permanent irreversible cirrhosis Animal experi ments have clearly brought out this point Discontinuance of the toxic substance at certain stages would result in complete recov ery but continuance beyond a certain point results in irreversible cirrhosis (Bollman)

Specific Detoxifying Agents

The use of specific detoxifying substances is an attractive therapeutic approach but one not easily attained Bal (British anti lewisite 2 3 dimercaptopropanol) is an effective antidote to lewisite Apparently it has some protective action against other compounds of arsenic as well as against mercury and other heavy metal poisoning As was mentioned arsenic achieves poisoning by attaching itself to sulfhydryl groups of cellular proteins thus arresting certain essential enzymatic processes Apparently Bal combines with arsenic to form a relatively nontoxic substance and prevents it from tying up with the essential sulfhydryl group Bal can be administered intramuscularly in 10% olution in doses of 3 0 mg per kilogram every four hours Longscope and Luetscher reviewed this problem of the antitoxic effect of Bal to various heavy metals Bal may be useful in gold and antimony intoxication however it is of doubtful value in nonmetallic poisons In phosphorus poisoning it is considered useless or even injurious (Diaz Rivera et al)

Dietary Protection of Liver

The use of specific agents to protect the liver from injury is in order Animal experiments have abundantly demonstrated the protective effect of high protein and high carbohydrate diets and the deleterious effect of high dietary fat Such diets are to be used in the treatment of toxic hepatitis If the patient is too ill to take oral feedings parenteral administration of glucose amino acids and plasma should be resorted to Methionine and methionine with cysteine have been shown to have a protective effect against experimental chloroform and carbon tetrachloride poisoning (Drill and Loomis Miller et al) This however appears to be true only if the animals have been on a protein-deficient diet Eddy successfully treated a group of patients with toxic hepatitis due to trinitrotoluene and carbon tetrachloride with methionine and high protein diet It may be questioned whether supplementary methionine is needed when a high protein diet is ingested ince such a diet contain an abundance of this amino acid The use of this amino acid is certainly indicated when dietary intake is not adequate Six to eight grams of methionine may be given daily in divided doses The use of methionine an amino acid with a sulfhydryl group is provocative in view of the affinity of some of the protoplasmic poisons for the —SH group which is so important in vital cellular enzymatic processes (For further discussion of methionine see pp 290–311)

Treatment of Specific Chemical Alterations

The combating of hypoglycemia and hypoprothrombinemia and hypoalbuminemia which frequently follow or accompany toxic necrosis of the liver is essential in the therapeutic regimen The hypoglycemia and hypoalbuminemia can be handled by replacement therapy The hypoprothrombinemia due to severe parenchymal damage will not respond to vitamin K therapy but may be aided by blood transfusions

VI The Effect of Infectious Agents on the Liver

25 The Response of the Liver to Infectious Agents and Pyrexia General Considerations

The liver may become involved by members of the entire spectrum of infectious agents from the ultramicroscopic virus to the grossly visible Metazoa Among the viral diseases that involve the liver are (1) infectious and homologous serum hepatitis (2) yellow fever and (3) infectious mononucleosis * Spirochetal involvement of the liver is exemplified by (1) Weil s disease (2) syphilis of the liver and (3) relapsing fever Nearly all bacteria pathogenic for man may involve the liver directly or indirectly Protozoal involvement of the liver is exemplified by (1) malaria and (2) amebiasis Metazoa do not spare the liver as is seen in the case of (1) schistosomiasis infestation (2) infection with Clonorchis sinensis and (3) Echinococcus disease (Table 37)

The involvement of the liver may be primary or secondary depending upon the infectious agent Thus the hepatic involvement may be responsible for the entire clinical picture or may be only a complicating factor Examples of this varying emphasis are found in all the groups of infectious agents Infectious hepatitis homologous serum hepatitis and yellow fever are examples of *viral disease that involve* primarily the liver although some renal involvement may be seen in all but especially in yellow fever Infectious mononucleosis *probably a viral disease is primarily a disease* of the reticuloendothelial system but involves liver injury so frequently that it is looked upon by some as a primary liver disease In Weil s disease the involvement of the liver is a primary feature but the renal involvement is of equal importance In the other spirochetal diseases—relapsing fever and syphilis—the hepatic involvement is of less importance In the former it is still a frequent occurrence in the latter a rare complication Bacterial involvement is almost always secondary to involvement of other organs however as occurs occasionally in tuberculomas of the liver and pyogenic abscesses of the liver the primary focus is undetected or clinically insignificant In brucellosis liver involvement is so common that it is a diagnostic feature of the disease While amebiasis and malaria are not primary diseases of the liver amebic abscess of the liver is such an important complication and hepatic dysfunction in malaria is so frequent that both diseases bring to mind the possibility of liver damage Schistosomiasis mansoni and japonicum and infestation with Clonorchis sinensis are of primary importance to the clinician because of the liver involvement while involvement of the intestines is of secondary importance Echinococcus cysts are rare in the United States When they do occur they are usually localized in the liver The hepatic involvement

* Viral origin not proved

TABLE 37

Infectious Agents Involving the Liver

Organism	*Disease*
Virus	Infectious } Hepatitis
	Homologous serum } Hepatitis
	Yellow fever
	Infectious mononucleosis
Spirochete	Weil's disease
	Syphilis
	Relapsing fever
Bacteria	Any bacterial disease may have hepatic component
	typhoid
	pneumonia etc
	undulant fever especially
Protozoa	Malaria
	Amebiasis
Metazoa	Schistosomiasis
	Clonorchiasis
	Echinococcus disease

is usually the most important clinical feature of the disease

The nature of the hepatic damage the manner in which it is produced and its ultimate *fate are variable and important features* In the case of viruses that attack the liver directly diffuse parenchymal necrosis is the characteristic lesion In many bacterial diseases focal degenerative changes may occur in the liver *without the presence of micro organisms* in this organ The liver injury may be produced indirectly by bacterial toxins or other factors or perhaps the organisms are disposed of by the Kupffer cells after the damage is done The rarity of suppurative lesions in the liver from systemic infections by pyogenic organisms is a curious feature A granulomatous response is seen in tuberculosis syphilis and brucellosis The flukes evoke a fibroblastic response

The ultimate fate of these various forms of injury are important especially in regard to their status in the production of cirrhosis Several broad principles may be laid down in regard to this Cirrhosis is more likely to result (1) from diffuse lesions (2) from lesions that disrupt the reticulum framework (3) from repeated rather single injuries and (4) when complicating dietary factors are present

Most acute infections that do not specifically or selectively affect the liver nevertheless impair this organ both functionally and structurally Indeed it is surprising that this involvement is not more extensive and frequent than it is The liver with its rich circulation gets more than its share of circulating micro organisms however they rarely gain a foothold and suppurations are uncommon The normal human liver is apparently sterile in most instances (Sborov et al) This may be due to a specific resistance of the parenchymal cells against bacterial invasion and to the phago cytic properties of the Kupffer cells which ingest and destroy the invaders

PATHOLOGY

Degenerative changes in the parenchymal liver cells are commonly found in patients dying from acute bacterial infections Cloudy swelling is an early change and actual necrosis *may* occur The latter may be especially prominent in overwhelming in fections Some fatty changes may likewise be ob served Such changes occur not only in the pneu monias *but in* typhoid fever septicemias and Rocky Mountain spotted fever Focal necrosis throughout the liver with organisms demonstrable in these areas has been described in streptococcic septice mias Such lesions *are reproducible* by *injection* of organisms into the portal vein of experimental animals

Morphological changes in the liver have been described in several fatal cases of artificial hyper thermia Bragden (1947) published a complete de scription of such a case Grossly the liver may be larger or smaller than normal Microscopically there is marked disturbance of the liver architec ture areas of complete loss of parenchymal cells are interspersed with areas showing regeneration The collapsed stroma contain occasional degenerated liver cells some of which are fatty and laden with pigment The degenerating cells are distributed in disorganized masses Occasional cells show inclusion bodies Between these pigment laden macrophages are noted Bile pigment is present within paren chymal cells and within canaliculi The portal areas show evidence of multiplication of bile capillaries lymphocytic infiltration and perhaps slight fibro blastic proliferation

Cirrhosis

These changes are acute they appear to be tran sient and should *not be expected to result in perma* nent irreversible liver disease However Phillips reported a multilobular cirrhosis in a 30 year-old patient who had been suffering from repeated staphy lococcic infections for a period of eight years There was no history of alcoholism nutritional deficiencies *or other demonstrable causes of cirrhosis The pos*

sibility naturally arises that the prolonged infection may have been of considerable importance in the pathogenesis of the diffuse chronic liver disease

Moon (1929) reported two cases of juvenile cirrhosis the liver in one case contained an unidentified coccus and in the other Streptococcus hemolyticus While etiologic significance was attributed to these organisms it is more likely that septicemia involved an already cirrhotic liver MacMahon used the term infectious cirrhosis in reference to an inflammatory process arising in the biliary tree He distinguished this entity from biliary cirrhosis since in the former obstruction is a transient feature This inflammatory process arising from the bile ducts i e ascending cholangitis may result in parenchymal necrosis loss of normal architecture bile duct and fibroblast proliferation This morphologic picture may be indistinguishable from other forms of cirrhosis

Pathogenesis

It seems worth while to analyze briefly the mechanism by which the liver is injured in the infectious and febrile conditions We are not concerned at the moment with the formation of abscesses which requires no elaborate explanation and is discussed elsewhere (Chapter 26) That the liver should be attacked by bacteria circulating in the blood stream is to be expected The liver should theoretically be more vulnerable than other organs since it has been demonstrated that this organ acts as a filter and removes circulating bacteria The bacteria may have a toxic effect on the liver

Anoxia is known to have a deleterious effect on the liver This has been demonstrated by perfusion experiments by De Lorme in studies on shock (Ellenberg and Osserman) and in congestive heart failure This factor may be especially important in pneumonia when anoxia may occur However in pneumococcic peritonitis degenerative changes are also found in the liver It seems likely that the bacteremia is more important than the pulmonary involvement per se

That *pyrexia* causes a disturbance in hepatic function has been demonstrated by Bradley and Conan by means of hepatic venous catheterization These normal subjects in whom pyrexia was induced showed a marked rise in hepatic blood flow (300%) but the bromsulphalein clearance decreased by 50%

The injurious effects on the liver from hyperpyrexia may be deduced from the experience with artificial fever therapy and heat stroke It has been suggested that the liver like the brain may be sensitive to high body temperatures Perfusion of the liver with hot saline can apparently injure this organ (Rawlison and Kellaway) Exactly how high body temperatures damage the liver is not known At least in clinical cases of prolonged fever the added demand on the liver coupled with relative insufficiency of foodstuffs and oxygen and with circulating toxins may act synergistically to injure the liver

Pathogenesis of Jaundice

Like the liver damage in febrile diseases the jaundice has been attributed to various causes In *pneumonia* the incidence of jaundice varies a good deal Klemperer reported 6 6% at Mount Sinai Hospital of New York Zimmerman and co workers 14% at Gallinger Hospital and Turner and co workers 67 7% at the George W Hubbard Hospital The high rate of jaundice in pneumonia in the last report is significant from the point of view of pathogenesis One concept formerly proposed in this regard was that right lower lobe pneumonias were more commonly associated with jaundice the latter being due to fixation or decreased mobility of the right diaphragm with resulting decrease of bile drainage This is mentioned merely for its possible historical interest because it is no longer seriously considered

Obstruction of larger bile ducts due to cholangitis or anatomical changes in the duodenum have also been proposed but have not been corroborated by either clinical or anatomical evidence The question actually resolves itself into whether the jaundice is due to *hemolysis* increased production of bilirubin or to *hepatocellular damage* The hemorrhagic exudate into the lungs and bronchi is hemolyzed and absorbed and thus adds to the bilirubin formed However this slight increase of bilirubin formation would hardly be sufficient to overwhelm a normally functioning liver Also pneumococcic bacteremias are accompanied by jaundice even in the

absence of hemorrhagic exudates Moreover there is anatomical evidence of parenchymal cell damage as well as laboratory evidence of disturbed liver function Thus there is little doubt that the jaundice is hepatocellular in origin but this may be slightly increased by the increased bilirubin formed

It has been thought in the past that jaundice occurs in the more seriously ill patients and therefore is a poor prognostic sign This viewpoint however is not held by others Zimmerman and Thomas found no correlation between the severity of the disease and jaundice or degree of hepatic impairment From a teleological point of view one would expect that the severity of the fever as well as the virulence of the infection should contribute to the degree of liver damage On the other hand severe liver damage which may be accompanied by marked icterus should be expected to have an unfavorable influence on the original disease In addition the nutritional state of the patient as well as pre existent liver injury should influence the picture Thus the very high incidence of jaundice in the Negro patients reported by Turner is attributed to their poor nutritional state This group also showed that experimental pneumococcic infection in dogs was more likely to result in liver injury when the animals were on an inadequate diet especially one lacking in the B complex Again we see the synergistic effect of multiple hepatotoxic agents

The mechanism of jaundice in other infections and especially in septicemias is probably different from that of the pneumonias Thus in hemolytic streptococcic septicemia the degree of jaundice was not found to bear any relationship to the degree of liver damage seen histologically Gas bacilli (B welchii) and hemolytic streptococci apparently produce severe hemolysis with hemolytic anemia and hemoglobinuria The jaundice in these conditions is therefore prehepatic in origin owing to increased bilirubin production However the anemia anoxia and toxemia may produce hepatic injury secondarily

Pathology—Summary

(Induced fever)

Size—larger or smaller

Microscopic

Disturbed architecture
Loss of parenchymal cells
Regeneration
Collapsed stroma
Fatty and pigment laden parenchymal cells

Portal areas

Multiplication of bile ducts
Lymphocytic infiltration
Slight fibroblastic proliferation

Cirrhosis

Occasionally attributed to repeated infections

Pathogenesis of liver damage

Toxic effect of bacteria
Anoxia
Pyrexia
Nutritional deficiency

Pathogenesis of jaundice

Hepatocellular damage
Increased hemolysis—contributory but of primary importance in hemolytic infections

LABORATORY FINDINGS

Along with the pathological changes described above and the development of icterus tests ordinarily used for evaluating hepatic abnormality show deviations from normal in acute infections MacLagan demonstrated that originally with his thymol turbidity test More recently Iversen and Raaschou found elevated thymol turbidity in a variety of acute infections This was especially frequent in measles but occasionally in tonsillitis scarlet fever meningitis and rheumatic fever While it is true that results of this test alone cannot be accepted as evidence of hepatic injury some degree of liver abnormality may be expected at least occasionally in many of these diseases

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performed and evidence of liver damage was found among some that showed no clinical jaundice In this report a correlation was observed between the degree of toxemia and the liver injury Jaundice and hepatic changes were reported by others and was produced experimentally (Buis and Hartman) In animal experiments infection was thought to play a minimal role since therapy was instituted immediately The clinical as well as experimental reports of liver damage in burns accompanied tannic acid therapy The decreased incidence of this complication since the change of therapy as well as the demonstrated hepatotoxic properties of tannic acid leads one to think that tannic acid was the responsible agent Previously the following factors were considered in the pathogenesis of hepatic damage in burns (1) shock (2) infection (3) pyrexia and (4) toxic tissue factor It is still likely that one or a combination of these factors plays a role in the occasional case that shows hepatic involvement

Pathology

The microscopic changes in the liver in most cases consisted of fatty degeneration necrosis of hepatic cells and sinusoidal hemorrhages The fatty changes are usually seen within the first 4 hours after injury The necrosis is located around the central vein and varies in intensity from very mild to very extensive leaving only the periphery of the lobule intact Lymphocytic and polymorphonuclear leucocytic infiltration about the portal areas is also noted In addition increase of pigment and mild degeneration of the cells of the bile ducts are occasionally present

Belt reported four patients dying from burns who showed hepatic necrosis simulating that found in yellow fever These patients were also treated with tannic acid The livers showed gross evidence of cloudy swelling the size was unchanged the color was yellowish resembling box wood which is characteristic of yellow fever Microscopically the necrosis was widespread but chiefly midzonal in localization Councilman bodies were numerous but smaller than in yellow fever Nuclear inclusion bodies were also prominent and occasionally assumed butterfly appearance These suggested the possibility of a virus being responsible for the lesion (Cowdry)

26 Pyogenic Liver Abscess

Abscesses of the liver are divided into two main groups amebic and nonamebic The latter is more commonly referred to as pyogenic liver abscess and is caused by a variety of organisms Amebic liver abscess is three times as common as the pyogenic variety This is surprising in view of the many different inflammatory processes that may give rise to this condition and the frequency with which bacterial infections can cause hepatic necrosis and degeneration With the advent of effective antibiotics pyogenic abscesses may even further decrease in frequency while the incidence of amebic abscess may not decrease because it originates from the insidious and frequently undetected amebic colitis

Another group of liver abscesses are those that arise from suppuration of a hepatic cyst or tumor Both parasitic and nonparasitic cysts may become secondarily infected to form an abscess Neoplasms may become necrotic in the center and eventually suppurate Disturbances in blood supply—both thrombosis and hemorrhage—may contribute to this complication

Incidence

The rarity of this condition is eloquently demonstrated by the statistics of Ochsner and

In *pne m o ia* o e exten e e aluat on of l ver f nct on by lal oratory means has been ca r ed out Curphe a d Solomon found progress ve abnorm al ty n the cter c ndex r nary rob l nogen and le ul se tolerance tests n f tal ca es of lobar pneun on a but rap d ret rn of tl e e tests to orm al n pat ents vho rec ered These o kers apparently sa v on e cor elat o bet een l er funct on and progno s n tl e r t dy Z n nerman and Thon s pe fo n c l n lj hale n clearance thym l u h cepha n flocculat on te p n w h pn mon a In 71 I he e e ca e l out in the 4 p l at on I th s group l oted n x vith the 4 6 th he cephal n l % tl tl e thymol en e est vere done later he e l e c of abnormal th a e pec all marked n Il e e b e ers d d not at o l et veen fever leuco l ev dence f sever ty of l l at c dysfunct on

a o 1 *Rocky Mo intain* l ed for ev dence of al dysfunct on by Wolff al eact ons vere not as l eu on a w th the except on the l ppur c ac d test Th s howed lecreased excret on of h ppur c ac d n 13 of 16 pat ents tested However s nce renal n pa rment was also detected n some of these tl e s gn ficance of th s test as regards hepat c abnormal ty is decreased (See section on L ver Funct on Tests) The prothromb n t me was prolonged n 5 of 11 patients Serum b l rub n was elevated n 1 of 13 pat ents The bromsulphale n test showed sl ght retention in 6 of 14 pat ents but in 2 pat ents th s was the only s gn of hepat c dysfunct on The serum prote n abnormal t es cons ste l of a decrease n album n n 18 of 24 pat ents wh le the globul n was elevated n 2 and decreased in two A decrease of the globul n is surpr s ng s nce it s usually not seen n hepat c d sease or acute nfect ons These abnormal t es were well correlated w th the cl n cal sever ty of the d sea e and usually were present at the peak of the llness

In *scarlet fe er* abnormal l er fun tion tests l ave been reported and these usually occur d ring the stage of comp cat o (Carsl a v and Creveld)

Treatment

It is stating the obv ous to say tha a spec fic antib otic if ava lable should be u ed for the treatment of the d sease and organ m nvolved By the use of such spec fic the ap the langer of damage to the l ver as we a other organs is m n m zed Ho veve along w th the spec fic therapy and e pe a y when such therapy is not ava lable and the illness is prolonged mea ures shou d be inst tuted to protect the l ver These should include bed rest and adequate ntake of prote ns carbohydrates and vitam ns espe c ally of the B complex group and a corbi ac d The nee l for these substances e en greater than n a healthy ind v dual fo w h fever there s an increase of the metabol c ra e and an increase of the detox f ng dema ds on tl e liver V tam n K should al o be ad min stered if the prothromb n t me s o- longed These measures not only hasten the patient s recovery from the acute lness bu m nimize the chances of ch on c sequelae Wh le there s no ev dence that these acu e nfect ons can term nate in c rrho s they ma conce vably aggravate a pre ex t ng chro c l ver d sease and the above mea u es may forestall such an eventua ty It al o ug gested that it vould be good cl n cal p a e to assay the state of the l ver n all acute illnesses by cl nical as ell as s mple labo atory tests Wh le other v tal organs such a he heart and k dneys are be ng watched he l ver s l kely to be neglected unless t becomes grossly enlarged or icterus appears I he cl n c an consc ously d rects h s atten on o th s organ wh ch may so frequentl b mpa red h s therapy w ll be mo e logical a d effective

Effect of Burns on the Liver

In severe extens ve burns both cl n cal and pathological ev dence of l ver damage has been observed Wilson MacGregor and S ewart found among 65 severely bu ned pa en 12 th jaund ce Twenty nec ps e were

3 Direct Extension of Infection

Direct extension from the gallbladder is a relatively common phenomenon Cholecystitis may be responsible for 6% to 14% of hepatic abscesses Other sources of direct extension are subphrenic abscess any type of localized peritonitis and intra abdominal abscess Even empyemas and perinephritic abscess may *occasionally* cause hepatic suppuration The inflammatory process involves and extends through Glisson s capsule Whether lymphatic spread is involved in these cases is a most important question Most students of this problem deny the importance of lymphatic spread in the genesis of pyogenic liver abscess

4 Trauma as Source of Infection

Trauma—both penetrating and nonpenetrating—may be the cause in a considerable number of cases Unusual cause of liver absce s are those due to penetration of foreign bodies into the liver substance such as pins (through the stomach into the liver) fish bones pieces of glass and straw (Ochsner et al)

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The biliary tract may serve not only as a source of infection but also as a pathway for transporting bacteria into the substance of the liver Suppurative ascending cholangitis may terminate in multiple liver abscesses This chain of events is usually preceded by



Fig 6 I y gen hep tic bsce se Light are on cut s rf ce of l er sh w ab ce areas The ab cess fol lowed pe for tions of acut empy m of th gall bl dd r w th ch l l thia Th pati nt g 56 had attacks of r ght pper abd m l p f r 4 m nth rad at g to the right cap l f ch ll nd jaund ce ff a d o l r 4 m nths Phy ical xam t n r al d ct ru f er of 104 r les in the right lung b se l r wa en l g d and te de le n w s palp ble Th m l tu b d ty unt S r m b l rub n 5 3 mgm% C ph lin chole terol flocc lat n 3 pl s Alkal ne ph ph tase 16 6 Bodan ky un ts T tal p te n 5 1 g ams Altumin 4 gm Gl b l n 7 gms. WBC 25 800

co-workers. At the Charity Hospital in New Orleans they found only 4, or 0.0077%, pyogenic abscesses of the liver out of 540,776 admissions. Collins reported an autopsy incidence of 0.606 [illegible]

Pathogenesis

The pathways by which the micro-organisms reach the liver [illegible] the site of origin may be summarized[1] [illegible]

1. Th[illegible] [illegible] infection from the [illegible]
   a. [illegible]
   b. [illegible]
   c. [illegible]
   d. stomach
   e. pancreas
   f. spleen
2. The hepatic artery bring[illegible] organisms from the systemic circulation in cases of
   a. pyemia
   b. bacteremia
   c. bacterial endocarditis
3. Direct extension from any adjacent organ or area
   a. gallbladder
   b. stomach
   c. right kidney
   d. subphrenic abscess
   e. localized peritonitis
4. Lymphatic spread from adjacent areas as in #3
5. Trauma
   a. penetrating by implanting the organisms
   b. nonpenetrating by producing hemorrhage or tissue damage which attracts infection
6. Biliary system infection arising from the larger extrahepatic bile ducts or from the gastrointestinal tract

1 Portal Vein as Pathway of Infection

The gastrointestinal tract is the most frequent source of pyogenic liver abscess. Of the various sections of the gastrointestinal tract the appendix is the commonest contributor to hepatic suppuration. Appendicitis has been found the primary cause in 11% to 24% of cases. The suppuration involves the appendicial veins, spreads to the ileocecal veins, thence to the superior mesenteric and finally the portal veins. Thrombophlebitis extends upward till the portal vein is involved. Pylephlebitis therefore precedes the liver abscess and the term pylephlebitic liver abscess is frequently used. The suppura[illegible] clot softens and small septic emboli lodge in the liver. The inflammation may also ex[illegible] through the vessel wall, thus involving the hepatic parenchyma. Because of "s[illegible] lining" of portal blood flow, bacteria from the superior mesenteric vein and hence from the appendix lodge in the right lobe of the liver. However, left lobe abscesses have been reported from appendicitis. These are [illegible] likely to be multiple.

Other diseases of the gastrointestinal t[illegible] that may be complicated by liver absc[illegible] include peptic ulcer, regional enteritis, ulcera[illegible]tive colitis, diverticulitis, carcinoma, esp[illegible] of the colon with ulceration and suppuration, proctitis and inflamed and thrombo[illegible]d hemorrhoids. All these diseases alon[illegible] with suppurations of the spleen and pancrea[illegible] are responsible for fewer liver abscesses than the appendix alone. Regional enteritis is a rare cause of pyogenic liver abscess. Crohn did not see o[illegible] case of this type in his extensive experien[illegible] with this disease and referred to only one case reported by Snavely. Another case has rec[illegible] been reported by Taylor. Ulcerative c[illegible] is also a rare cause of pylephlebitic ab[illegible] of the liver and is apparently commone[illegible] a[illegible] ileostomy (Bockus). Treusch recently repo[illegible] multiple liver abscesses in a young wom[illegible] with fulminating ulcerative colitis. Rare[illegible] bacillary dysentery or typhoid f[illegible] may result in liver abscess. Hirschowitz [illegible] reported a case of solitary liver ab[illegible] cau[illegible] by Salmonella enteriditis and found only one other case in the literature.

2 Hepatic Artery as Pathway of Infecti[illegible]

Distant foci of infection outside of the port[illegible] area deliver the bacteria through the hep[illegible] artery. These may include osteomyel[illegible] bacterial endocarditis and any other s[illegible]ppura[illegible]tion that may result in bacteremia or pyem[illegible] These distant foci were the cause in 11% [illegible] Ochsner's collected series

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5 Biliary Tract as Pathway for Infection

The biliary tract may serve not only as a source of infection but also as a pathway for transporting bacteria into the substance of the liver Suppurative ascending cholangitis *may terminate in multiple liver abscesses* This chain of events is usually preceded by



Fig 26 Fy g ni h p t c b c se Lght ar s n cut s rf ce of l r sh w ab cess areas The ab cess fol lowed perf rat ons f ac t emp m of the gall bladd r w th ch l l thia i The p t nt age 56 h d attacks of right pper abd m n l pa n f 4 m nth radiati g to the right sc p la f ch ll nd ja nd c ff a d on f 4 month I h ical exami at re ealed ict n f e f 104 rales in th r ght l g base l ver was en l ged a d te d r pl en was palp ble Th m l t rb d ts u it Serum b l r b n 5 3 mgm% Cephal n chol t l fl xc lat on 3 pl Alkaline ph ph t se 16 6 Bodan k n ts T tal p t n 5 1 gr ms Alb m n 4 gm C l b l n 7 gm WBC 5 870

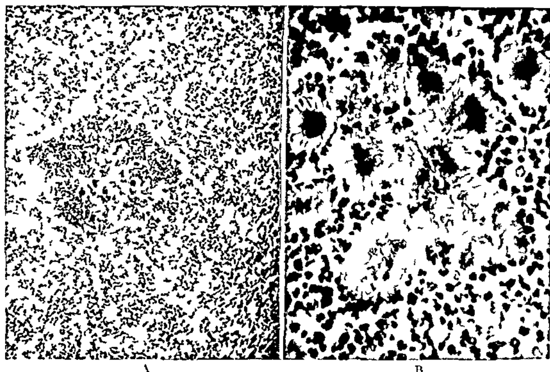


Fig 7 Actinomycosis of liver showing the ray fungus and intense exudative reaction A low power magnification B high power magnification (Courtesy Dr Pirani Dept Pathology University of Illinois School of Medicine)

cholelithiasis and obstruction of the common bile duct (Fig 26) An unusual case of invasion of the liver by ascarides via the bile ducts is quoted by Ochsner and co workers

6 Source of Infection Unknown (Cryptogenic)

There is finally a large group of liver abscesses in which the primary focus remains undetected 59 5% of the New Orleans Charity Hospital series were in this category This has been referred to as cryptogenic idiopathic or primary pyogenic hepatic abscess It may be due to a small and insignificant focus drained by the portal vein or discharging its contents into the systemic circulation These cryptogenic abscesses are more likely to be solitary

Bacteriology

The organisms that most commonly cause pyogenic liver abscesses are Escherichia coli streptococci and staphylococci Other organisms occasionally cultured from these abscesses include pneumococci B subtilis Alcaligenes faecalis diphtheroids B pyocyaneus Aerobacter aerogenes Leptothrix actinomyces (Fig 27) Streptothrix Histoplasma Eberthella typhi Salmonella Shigella spirochetes and gonococci Recently a case of probable liver abscess due to Bacteroides funduliformis was reported by Rubin and co workers Beukema reported a liver abscess due to Giardia lamblia The abscesses are sterile in 38% to 60% of cases

Types of Liver Abscess

1 Amebic (Tropical)—due to E histolytica

2 Nonamebic (Pyogenic)

Bacteriology
- E coli, Streptococci, Staphylococci } Commonest

Other Organisms
- Pneumococcus
- B subtilis
- Alcaligenes faecalis
- Diphtheroids
- B pyocyaneus
- Aerogenes

F typhi
Salmonella
Shigella
Spirochetes
Gonococci
Bacteroides funduliformis
Giardia lamblia
Fungi
Leptothrix
Streptothrix
Histoplasma
Actinomyces

Pathology

The liver is usually moderately enlarged Multiple abscesses are commoner than solitary abscesses In either case the right lobe of the liver is more commonly involved than the left lobe This speaks for the stream lining of the portal blood flow which is the commonest pathway of bacteria reaching the liver In Rothenberg and Linder s series the right lobe was involved five times more frequently than the left lobe In Ochsner and co worker s series the right lobe was involved in 68 1% the left lobe in 2 % and both lobes in 27 % of cases Not in all series of cases do the multiple abscesses exceed the solitary ones This is exemplified by Ochsner s own series in which over half were single but in the collected series only 28 8% were single

When multiple abscesses are present the liver has a mottled appearance The involved areas may be firm and suggest metastatic malignancy They vary from 0 5 to 1 0 cm in diameter Small multiple abscesses may coalesce to form one large abscess One of Beaver s abscesses was 15 cm in diameter containing 1 00 cc of pus The inflammatory process may involve Glisson s capsule and may cause adherence of the liver to the diaphragm The process may extend through the diaphragm resulting in an empyema pneumonia or lung abscess

Suppurative processes may be found which started the liver abscess Thus the empyema or the perinephritic or subphrenic abscess may have antedated the liver abscess On the other hand the abscess may rupture resulting in localized or generalized peritonitis or subphrenic abscess In Keefer s series these complications were present in 8% and 6% respectively Rare complications of pyogenic hepatic abscesses are ruptures into the pericardium into the thoracic duct and into the inferior vena cava

Microscopically the liver tissue adjacent to the abscess may show evidence of necrosis and infiltration with inflammatory cells The capsule is usually not thick except in the chronic abscesses as described by Beaver when a very thick fibrous capsule may form The capsule may consist of compact fibrous tissue and endothelioid cells as well as foreign body and Langerhan s type of giant cells forming a granulomatous mass

When the pylephlebitic type of abscess is present a soft septic thrombus may be found in the portal vein The vein is dilated and may show localized bulging Small perforations of the vein may be found Microscopically the septic process will be identified in the lumen as well as in the vessel wall

Pathology—Summary

Liver moderately enlarged
- **Multiple abscesses commoner**
- **Right lobe most commonly involved**
- **Appearance—mottled**
- **Consistency—if firm very suggestive of neoplasm**
- **Size**
  - **0 5 to 1 0 cm in diameter—multiple**
  - **15 cm in diameter—solitary**
- **Extension to**
  - **Glisson s capsule**
  - **Subphrenic space**
  - **Through diaphragm—to cause**
    - **Empyema**
    - **Pneumonia**
    - **Lung abscess**
    - **Pericarditis**
  - **Rupture into**
    - **Thoracic duct**
    - **Inferior vena cava**
- **Microscopically**
  - **Adjacent liver tissue shows necrosis or inflammatory cell infiltration**
  - **Capsule**
    - **Thick in chronic abscesses consisting of**
      - **Fibroblasts**
      - **Endothelial cells**
      - **Giant cells**
  - **Pylephlebitic type—shows infected thrombus in portal vein**

Clinical Features

The sex incidence shows a preponderance of males in a ratio of approximately 2 1 The incidence as to age shows a wide distribution from infancy to advanced age The age of predilection varies in different series from young adult to the fifth decade of life

Signs of sepsis dominate the clinical picture

Chills fever and drenching perspiration are usually present The fever is usually intermittent of the picket fence type but may be continuous Signs and symptoms of the primary disease may precede development of the pyogenic liver abscess Thus in a patient who *starts out with acute appendicitis and* then has shaking chills and high fever pylephlebitis and liver abscess should be suspected

Weakness anorexia loss of weight nausea and vomiting are less frequent symptoms Pain in the right upper quadrant of the abdomen is almost always present It may vary in intensity and may be aggravated by cough or deep breathing This is especially common in right lobe abscess irritating the dome of the diaphragm Pain may also extend to the neck or the right shoulder This may be due to irritation of the diaphragm or *involvement of the pleura* Chest pain and cough may be present because of extension of process into the right thoracic cavity

Liver tenderness and enlargement is almost always present The tenderness may be localized or diffuse depending upon the extent of the process and may be exquisite in the acute process The hepatic enlargement may be both up and down The elevation and immobility of the diaphragm may be detected by physical examination

Examination of the chest may reveal dulness rales or a friction rub in addition to diaphragmatic changes

Jaundice is an uncommon finding and was observed in only 8% of Rothenberg and Linder s series and 25% of Ochsner s series Jaundice is considered a poor prognostic sign It is usually not intense and is most likely due to compression and edema of the hepatic duct However parenchymal cell dysfunction may undoubtedly occur because of the fever sepsis and interference with the intake of food Ascites is rarely found in this condition but has been reported When it occurs it undoubtedly depends upon the *thrombotic obstruction of the portal vein plus* serum protein depletion

Clinical Features—Summary

Sex incidence—Preponderance of males

Age—Infancy to advanced age

Signs of Preceding Disease Followed by

- **Sepsis—chills, fever drenching sweats**
- **Pain in right upper quadrant or chest**
- **Cough**
- **Liver enlargement and tenderness**
- **Elevation and immobility of diaphragm**
- **Jaundice—not common—8%–25% of cases**
- **Ascites—rare**

Laboratory Findings

A marked *leukocytosis* with a preponderance of polymorphonuclear leukocytes is a characteristic feature of pyogenic abscess of the liver The leukocyte count may be as high as 50 000 cells per cubic millimeter and is usually above 20 000 however in the more chronic abscesses leukocytosis may be only moderate or even absent A mild secondary anemia may be present

In bacteremia the causative organism may be cultured from the blood

X ray is valuable in detecting an elevated and fixed right diaphragm Ochsner and co workers have re emphasized the difference in the diaphragmatic contour between liver abscess and subphrenic abscess from other causes In the former there is obliteration of the cardiophrenic angle in the anteroposterior roentgenogram and obliteration of the anterior costophrenic angle in the lateral view while in the latter there is an obliteration of the costophrenic angle in the anteroposterior view and obliteration of the posterior costophrenic angle in the lateral projection

Miles has described pressure deformities of the lesser curvature and the cardia of stomach as well as the duodenal cap These are produced by abscess on the inferior (concave) surface of the liver

Liver function tests are not extensively reported in the literature The icteric index is usually only slightly elevated but in cases of abscess *arising from suppurative cholangitis* may be very high because of the accompanying complete biliary obstruction In the case reported by Rubin et al the icteric index reached 150 units In their case the alkaline phosphatase was also markedly elevated in

addition the thymol turbidity was positive the cholesterol esters were depressed and the globulin was elevated In a case such as theirs with diffuse involvement and long duration extensive parenchymal damage is to be expected In the ordinary case however the liver profile would probably not be so abnormal An elevated alkaline phosphatase and slight retention of bromsulphalein can be expected

The urine contains bilirubin in the jaundiced case Albumin may be present occasionally Urobilinogenuria may also be increased

Laboratory Features—Summary

Leukocytosis marked with preponderance of polymorphonuclear cells

Bacteremia

X ray and fluoroscopy
Elevation and fixation of diaphragm
Pressure deformity of stomach

	Liver abscess	Subphrenic abscess
AP view	Cardiophrenic angle obliterated	Costophrenic angle obliterated
Lateral view	Anterior costophrenic angle obliterated	Posterior costophrenic angle obliterated

Liver function tests
- **Serum bilirubin slightly elevated high if secondary to cholangitis**
- **Alkaline phosphatase elevated even in absence of jaundice**
- **B S P retention**
- **Flocculation tests occasionally abnormal**
- **Globulin may be elevated**
- **Urine bilirubinuria**
- **Hyperurobiligenuria**

Diagnosis

The diagnosis is based upon an antecedent infection the development of chills fever hepatic tenderness and enlargement the marked leukocytosis and roentgenographic findings The differential diagnosis will be discussed under Amebic Abscess

Treatment and Prognosis

In the past the mortality from pyogenic abscess of the liver was 50% to 95% However since the advent of chemotherapy and antibiotics the prognosis should be much more favorable This is supported by the recent experiences of Flynn Kisner Rubin and co workers If the causative organism is determined it should be subjected to sensitivity tests and the appropriate antibiotic administered If the causative organism is unknown a broad spectrum antibiotic or combination of antibiotics should be administered Penicillin streptomycin aureomycin terramycin and chloromycetin would all have a place in various situations

Surgical treatment is directed first to the prevention of pylephlebitis The appendiceal ileocecal superior mesenteric and portal veins should be inspected during an appendectomy when chills and fever have been experienced Ligation of the smaller veins and even the superior mesenteric has been done without untoward results (Stewart Wallace) If a thrombus is present in the portal vein its evacuation is advised

Evacuation of a solitary large abscess is recommended This should be done without contaminating the pleural or peritoneal cavity Ochsner advises an extraserous anterior or posterior approach which is discussed in that publication The pus obtained should always be cultured so that the most effective antibiotic therapy can be utilized

The more adequate treatment of the primary disease with antibiotics will undoubtedly decrease the incidence of pylephlebitis and liver abscess

27

Amebic Abscess of the Liver (Amebic Hepatitis)

Incidence

Involvement of the liver by the Entameba histolytica is the commonest extra intestinal complication of amebic colitis It is more common in regions where amebiasis is most prevalent It has been estimated that 5% of patients with amebiasis may develop hepatic complications If this were calculated on the basis of the 10% incidence of amebic infection estimated by some we should expect three fourths of a million cases of hepatic amebiasis The actual incidence is much lower than this Immediately after World War II we saw 15 cases of hepatic amebiasis in veterans who served in the South Pacific in a large Veterans Hospital within a nine month period Since then this high incidence has dwindled to an occasional case

It must be emphasized that amebiasis is a ubiquitous disease and the disease and all of its complications may be encountered in any part of the world It is nevertheless true that this disease like other parasitic infections is more common in tropical and subtropical areas

Etiology

The invasion of the liver by Entameba histolytica is secondary to the intestinal disease There is no primary amebic hepatitis or amebic abscess of the liver The cysts are ingested by the host and the active trophozoites penetrate the bowel wall to form ulcers The most common site of amebic ulceration is in the cecum The parasite destroys the tissues of the host by a cytolytic process blood vessels may be eroded in the process This may result in hemorrhage or dissemination of the parasite to distant areas The erosion of a venous channel leads to the spread via the portal vein into the liver From the stream lining of the portal venous current it can be surmised that material from the cecum is more likely to reach the right lobe of the liver

The time interval between the onset of the intestinal disease and its hepatic complications varies a great deal It is rarely under six months but may be as long as 57 years (Mansohn Bahr) Therefore a patient with intestinal amebiasis is never safe from an hepatic abscess

What precipitates spread of the infection to the liver? The virulence of any infectious disease depends on the resultant of two opposing forces the virulence of the invading parasite and the resistance of the host A breakdown of the defensive barrier or increased virulence of the ameba may result in its dissemination Trauma to the abdomen may be a factor This could result in mechanical dissemination of the parasite Alcoholic indiscretion has been considered a possible precipitating factor Over work over exertion or anything that may lower the resistance of the host may invite this serious complication Occasionally no precipitating factor can be determined

Etiology—Summary

Incidence is ubiquitous high in tropical areas
Colonic disease always primary
- **Trophozoite erodes venule carried via portal vein into liver**
- **Time interval between primary infection and complication—6 months to many years**

Precipitating factors
- **Lowered resistance of host**
  - **trauma**
  - **alcohol**
  - **fatigue**
  - **malnutrition**
- **Increased virulence of parasite**

Pathology

The liver is increased in size and this depends on the size of the abscess Usually only the right lobe

is enlarged since it is the most frequent site of the abscess If several large abscesses are present the liver is irregular

The abscesses vary in size from very minute ones just visible to the naked eye to enormous cavities occupying the entire lobe One of the amebic abscesses we have seen contained 2200 cc of fluid Amebic hepatitis actually consists of minute or microscopic abscesses which if allowed to develop enlarge break down become confluent and form one large abscess

The location of the abscesses is chiefly in the right lobe (Fig 283) The left lobe abscesses account for about 15% and the rest are locat d in th right lobe About 70% of the abscesses are solitary and 30% multiple

The contents of the abscess cavities have a characteristic color unless invasion by bacteria has taken place The material is thick and brownish in color and has been referred to as chocolate sauce or anchovy paste This appearan e is due to the fact that the material is composed of debris from autolyzed liver cells and hemolyzed blood It is not pus since very few polymorphonuclear leucocytes are found in it It is ordinarily sterile as far as bacteria are concerned and the Entameba histolytica is found with difficulty Red cells and desquamated tissue cells are found in abundance

The wall of the abscess varies in thickness depending on its chronicity The larger older abscesses have a thickened connective tissue wall Its surface has a moth eaten appearance Microscopically the surface in contact with the abscess is covered by necrotic debris partially autolyzed liver cells and an occasional trophozoite of Entameba histolytica The organisms are found most readily in the necrotic areas Away from the surface of the abscess is a thick connective tissue membrane in which parasites are very infrequent In the connective tissue are numerous polymorphonuclear leucocytes and lymphocytes External to the fibrous band is a zone of hyperemia and thrombosed venous channels An occasional ameba may be found here also Further away from the abscess cavity is liver parenchyma showing some distortion and atrophy from pressure but adjacent to this area is normal liver parenchyma

The primary intestinal involvement may be healed or quiescent when the patient succumbs to the hepatic abscess However the intestinal disease may be very much active and show extensive ulceration At autopsy the intestinal lesions may be very extensive and show large shaggy superficial and deep ulcers and even some perforated ulcers with peritonitis This was the situation in one of our cases (Figure 8b)

The hepatic abscess which frequently points against the dome of the diaphragm perforates through the diaphragm resulting in empyema or more frequently in abscess of the lower right pulmonary lobe Brain abscess is a rare complication of amebiasis When it occurs it is associated with



Fig 8 A Photograph of diaphragmatic s rf ce of the right l be of the l ver demonstr t ng a l rge ameb c abs e B Colo f same pat e t show ng extens e ameb c col t

hepatic abscess We reported a cerebellar abscess in a patient with intractable recurrent liver abscess (Spellberg and Zivin)

The virulence of the infection or the breakdown of the defenses of the host may result in diffuse

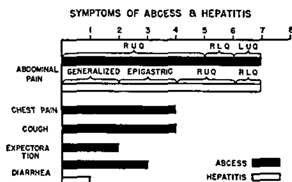


Fig 9 The frequency of various symptoms in 15 patients with amebic abscess and amebic hepatitis (From Spellberg & Zivin Gastroenterology *10* 45 1948)

dissemination of the infection This was noted in a case I have seen in which there was involvement of both lungs kidneys adrenals spleen as well as liver and perforation of the transverse colon The metastatic lesions were firm and rubbery like gum mata and did not show liquefaction (Fig 31a b c)

Pathology—Summary

Liver—increased in size depending on size of abscess

Right lobe is usually only lobe enlarged

Abscess

Location—85% right lobe 15% left lobe

Solitary—70%

Multiple—30%

Size Minute microscopic or very large (2000 cc +)

Contents

anchovy paste in color and consistency

microscopically debris desquamated liver cells and erythrocytes

sterile

amebae found in wall of abscess

Wall of abscess connective tissue—lymphocytes and polymorphonuclear leucocytes parasites

Associated pathology

colonic ulcerations extensive or absent

pulmonary abscess

brain abscess

Clinical Features

Both amebic hepatitis and amebic abscess of the liver present themselves as acute febrile illnesses The difference between the two is quantitative rather than qualitative The only clearcut difference is in their response to therapy which will be discussed later Patients have been described with chronic abscesses which have a lowgrade fever and the other symptoms are mild compared with the acute disease The chronic abscess may show acute exacerbation, and during these periods show the picture that will be described

Symptoms (Fig 29)

Abdominal pain is the commonest symptom and was observed in all but one of our 18 patients with amebic hepatitis and abscess The pain is usually dull and aching but may be sharp and stabbing The location of the pain is mostly in the right upper abdominal quadrant but it may be in the epigastrium right lower quadrant left upper quadrant or generalized

Chest pain is a frequent symptom in amebic hepatic involvement either because of direct extension to the lungs or because of irritation of the diaphragmatic pleura In the latter instance the pain is pleuritic in nature sticking and increased with respiration In one of our patients it was present without abdominal pain Pleuro pulmonary pain is more common in abscess than in hepatitis The chest pain may radiate to neck or right scapula

Cough may accompany the chest pain It is more likely to be present in abscess with perforation into the pleural cavity and hence

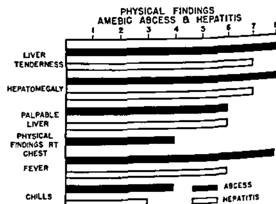


Fig 30 The frequency of various physical findings in 15 patients with amebic abscess and amebic hepatitis (From Spellberg & Zivin Gastroenterology *10* 4 1948)

t s f equently accompan ed by expectorat on The sputun may g e a clue to the d agnos In one of our pat ents the anchov paste character of the sputum led to the co rect d agno



F g 3 A Roen gen g m of ch of ea d pa how ng num ea o fi on p ov d a op o b d e o am b g n m

D arrhea s pre ent n les than half of the pat ents w th hepat c ameb as s Th s help to obscure the d agno Only three of our e ght pat ents w th ab cess had d ar hea an nc dence of 37% F ve were unable to recall d arrhea at any t me F ve pat ents v th hepat t recalled ep odes of d arrhea n the past The nc dence of d a rhea obser ed by othe s var es between 3 % and 48% of ca es (Berne 1943 Klat k n 946 Och ner et al Sodeman and Le s 1945)

Phys al F nd ngs (Fig 30)

L er tende ne s and l epatomegal were seen in all ou pat ent The tenderne s can be el c ted b palpa on and pe cu on Tender ness s pre ent n the ep ga tr u n and r ght hypocl ondr n Tenderness s frequentl el c ted n one of the lower ntercostal pa es n the m d or anter or ax lla l ne Th s tendernes may be finger po nt and nd cates po nt ng of the abscess and therefo e the s te of cho ce for asp rat on Exqu s te finger po nt tendernes s d agnost c of abscess format on and not fo nd n ameb c hepat t s





F g B Roen g nogr m o c on fi ed w h bari m s lf e pen n C Af er b um w s emp d The e \ d m e lar fi g d fec n n e er on a d fi la l ad g f om h a a

Hepatomegaly was found in all of our 15 cases but in only 12 was the liver palpable In the other patients the enlargement was upward and was detected by the elevation of the right diaphragm

Abnormal findings in the chest consist of dullness suppressed breath sounds crepitant rales and changes in fremitus The findings are usually confined to the right chest and are most marked in the patients who have pleuro pulmonary complications Involvement of the left lung may occur from left lobe abscess or from diffuse hematogenous metasasis (Fig 31)

Fever was a frequent and troublesome symptom and finding It was present in all our patients with abscesses and all but one of the patients with hepatitis It is usually septic in type and may be as high as 103 or 104 F In many cases the fever is accompanied by chills and drenching sweats

Jaundice is an infrequent finding and because of its mildness may be overlooked clinically and hence will be discussed under laboratory findings

Laboratory Findings (Fig 32)

Roentgenograms of the chest represent one of the most useful laboratory procedures for detection of hepatic amebic involvement Elevation of the right diaphragm and limitation of its mobility is an early constant and diagnostic sign Elevation of the diaphragm occurs in amebic hepatitis as well as amebic

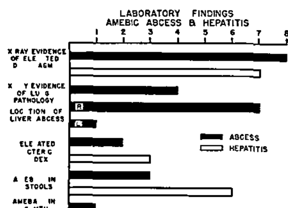


Fig 32 The frequency of various laboratory findings in 15 patients with amebic hepatitis and amebic abscess (From Spellberg and Zivin Gastroenterology 10 452 1948)

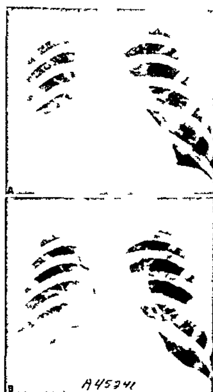


Fig 33 Roentgenogram of chest of patient with amebic hepatitis

A Shows marked elevation of right leaf of diaphragm

B Diaphragm is at normal level after emetine therapy

abscess and the degree of elevation does not differentiate the two conditions (Fig 33 and 34) A triangular elevation of the right diaphragm is a sign of abscess Blunting of the costophrenic or cardiophrenic angle from minimal pleural effusion may occur in either condition More extensive involvement of the right lung results from perforation of the abscess through the diaphragm This produces signs of consolidation and cavitation with fluid level (Fig 34 b) Lesions may be seen in both lungs but left lung involvement is rare The pulmonary roentgenographic signs have been discussed by many observers Schorr and Schwartz have recently pointed out an additional sign of pulmonary amebiasis This consists of a linear perpendicular shadow in the region of the right lower lobe

The finding of amebae in the stools is a great help in the diagnosis but is found in a minority of cases In our series the parasite was found in the stools in 60% of patients The incidence

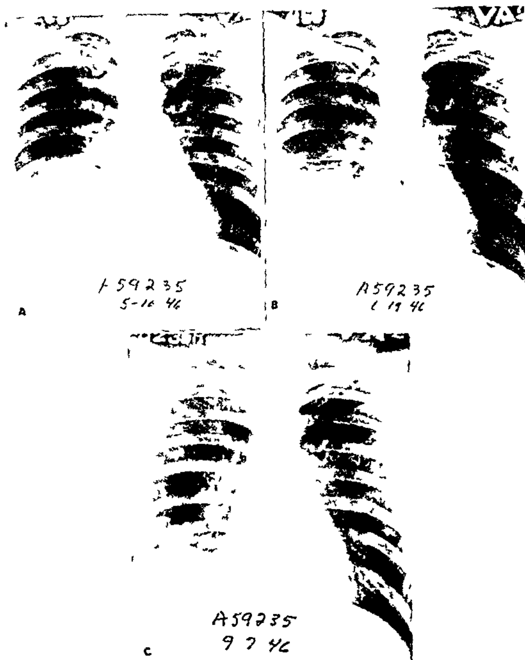


Fig 4 F ol t n f meb absc of the l with pe r t n into the right pleural ca ity
A Elevat n f right di phr gm
B O e month later sh wi g in l m nt of right lower l be ggest e of l ng ab ce s.
C After pecific therapy h wing cl ari g f i l ed pulmona y area

of positive stools in the literature is only 4 4% to 48 6% The parasite may be discovered in the sputum This occurred in one of our patients

The complement fixation test for amebiasis has been used from time to time with modifications since it was proposed by Craig in 1927 Recent observations confirm the viewpoint that in its present state this test is of doubtful clinical value because of the frequency of falsely positive and falsely negative results (Dolkart et al 1951 and Buchman et al 1952)

Leukocytosis is usually present and is of moderate degree usually below 20 000 One of our cases showed a leukocytosis of 28 000 A marked leukocytosis favors a diagnosis of pyogenic abscess

Liver function tests are either normal or show only moderate disturbance Hyperbilirubinemia is either mild or absent One third of our patients showed an elevation of the serum bilirubin This is higher than the incidence reported in the literature 19% in Ochsner s patients and 15% in Sodeman and Lewis series A moderately elevated alkaline phosphatase and mild bromsulphalein retention may also be detected Changes in the plasma proteins and abnormal flocculation reactions are rarely noted

Diagnosis

A greater awareness of amebic hepatic complications is necessary for a reduction of the failures in diagnosis The diagnostic features of the disease consist of abdominal especially right hypochondriac pain accompanied by fever chills hepatomegaly exquisite finger point tenderness in some area over the liver especially the lower intercostal spaces in the axillary region elevation with limitation of motion of right diaphragm A leukocytosis of moderate degree is almost always present Symptoms physical and roentgen findings referable to right lung may also be present When the above clinical data is elicited one of the specific drugs discussed below should be administered A prompt response clinches the diagnosis The complement fixation test remains of doubtful diagnostic value

Differential Diagnosis

The disease may be confused with other diseases of the liver pulmonary diseases and systemic infections It should be easy to differentiate it from infectious hepatitis In this disease fever, if present is low grade and there is no leukocytosis Liver tenderness is diffuse and the diaphragm is never elevated or fixed The liver function tests are markedly disturbed Cirrhosis may be similarly excluded

Diseases of the lungs such as pneumonia and empyema are frequently confused with amebic abscess of the liver because of the symptoms and findings referable to the right lung In these diseases all of the findings are supradiaphragmatic the liver is not enlarged nor tender and the diaphragm is not elevated If the liver is involved independently of the lungs differentiation may have to depend on the therapeutic response

Systemic diseases especially those accompanied by chills and fever may present a problem In one of our cases malaria was superimposed on an amebic hepatitis The recurrence of chills fever suggested that the liver infection had recurred But the leukopenia and splenomegaly led to an examination of a blood smear in which the parasites were demonstrated The absence of localizing symptoms or findings in the liver should lead to a search for other specific organisms in the blood stream urine etc

Pyogenic liver abscess has to be differentiated from the conditions mentioned above and from amebic abscess The antecedent disease as well as the marked leukocytosis help the diagnosis of pyogenic abscess The jaundice is also likely to be more marked

Subphrenic abscess can be diagnosed by the history of previous surgery intraperitoneal inflammation or perforation of a viscus the leukocytosis is marked the liver is not enlarged Some distinct roentgenographic findings were pointed out on page 190 which help to differentiate subphrenic abscess from hepatic abscess

Treatment

The treatment should be directed toward eradication of the liver abscess and eradication of the ameba from the intestine

Emetine Hydrochloride

The two drugs specific for amebic hepatic involvement are emetine hydrochloride and chloroquine diphosphate Neither of them is effective in the intestinal disease Emetine hydrochloride is administered subcutaneously in 0 065 gm (1 gr) doses daily for 10 to 12 days After a period of rest lasting two weeks one or two additional courses of treatment may be administered The effect of emetine on the fever and pain of amebic hepatic involvement is dramatic Within four or five days emetine therapy changes a very sick patient who has been markedly febrile for weeks into a comfortable individual who is either completely or nearly afebrile This effect is so specific and invariable that it can be used as a therapeutic test for amebic hepatitis and abscess (Fig 35) The drug should be continued for one course (10–12 days) If a lowgrade fever persists or returns on cessation of emetine it is an indication of an abscess rather than hepatitis The abscess cavity should be treated by aspiration

Certain precautions should be followed in the use of emetine This drug is potentially toxic and its serious toxic effects are on the myocardium and may lead to sudden collapse and death This toxic effect is only partially related to the dose but is chiefly due to an individual idiosyncrasy The patient therefore should be at complete bed rest have frequent

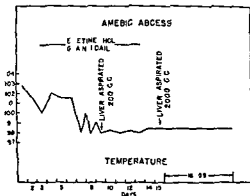


Fig 35 Temperature graph of a patient with amebic abscess of the liver showing the response to treatment (From Spellberg and Z ... 452 1948)

blood pressure and pulse rate determinations (every four hours) and an electrocardiographic tracing before therapy is started and every four days thereafter When signs of cardiac injury appear the drug should be discontinued

Chloroquine Diphosphate

This drug has been found to be very efficacious in amebic hepatitis and because of its lower toxicity may displace emetine as the treatment of choice (Conan 1949 Sodeman et al 1951 and others) This drug is used orally in 0 25 gm dose four times a day for three days and twice a day thereafter for fourteen days I have seen chloroquine succeed when emetine failed to produce a complete remission of symptoms

Closed Drainage

If emetine or chloroquine do not produce complete amelioration of symptoms disappearance of tenderness and appreciable reduction in the size of the liver aspiration by needle and syringe is indicated

Location of puncture 1 At the point of maximum tenderness which is frequently between the eighth and tenth interspaces in the anterior axillary line 2 If the abscess is anterior as demonstrated by lateral and anteroposterior chest x rays as well as by palpatory findings the puncture should be below the right costal margin 4–5 cm to the right of the xiphoid 3 If the abscess is posterior the puncture should be below the 12th rib to the right of the costovertebral angle

1% procaine infiltration anesthesia can be used The needle should be 16 or 14 gauge to allow for aspiration of the thick material A large Luer syringe at least 20 cc capacity but preferably 50 cc should be used By this means I have aspirated one 2,000 cc abscess with cure of the patient Sherry and co workers have advised the use of a mixture of streptokinase and streptodornase to liquefy the thick abscess contents which consist chiefly of extracellular desoxyribonucleoprotein This has been unnecessary in my experience

Aspiration should be followed by another course of emetine or chloroquine

Surgical Drainage

Surgical drainage is inadvisable because of its higher mortality and morbidity owing to secondary infection (Ochsner et al) Surgical drainage becomes necessary in multiple abscesses and solitary abscesses situated in the left lobe of the liver which cannot be aspirated readily

Intestinal Amebicides

In order to eradicate the disease completely and prevent recurrence of hepatic complications the colon must be cleared of the ameba Other amebicidal drugs have to be used which are effective against the colonic disease This should be done even when the stools are negative for amebae

The drugs that have proven amebicidal activity are the following

Diodoquin (5,7 diiodo 8 hydroxy quinoline) 0 63 gm four times a day for 20 days

Chiniofon (7 iodo 8 hydroxyquinoline 5 sulfonic acid) 1 0 gm three times a day for ten days

Carbarsone (carbaminophenyl arsonic acid) 0 25 gm twice a day for ten days

Milibis (bismuthoxy P N = glycolarsanolite) 0 5 gm four times a day for ten to fourteen days

Terramycin 0 25 gm four times a day for ten days

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Syphilis of the Liver

HUMAN infection with Treponema pallidum in its varied manifestations and its tendency to imitate other diseases involves the liver in several stages and produces different clinical and pathological features

Hepatic syphilis may be grouped under the following headings

- I *Congenital syphilis*
  - A Diffuse fibrosis (syphilitic cirrhosis)
  - B Gummatous involvement
- II *Acquired syphilis*
  - A Early acute involvement (syphilitic hepatitis)
    - 1 mild type (icterus syphiliticus praecox)
    - 2 severe type (acute yellow atrophy icterus gravis syphiliticus)
  - B Late (tertiary stage)
    - 1 focal involvement (gummatous syphilis) (hepar lobatum)
    - 2 diffuse involvement (syphilitic cirrhosis)
- III *Post therapeutic hepatic involvement*
  - A Toxic (heavy metal) hepatitis
  - B Homologous serum (syringe) hepatitis
  - C Jaundice associated with malarial therapy
  - D Cirrhosis following heavy metal therapy

Incidence

While in the experience of the average clinician hepatic involvement in patients with syphilis is an uncommon occurrence the liver is a common site of visceral involvement Visceral gummas are common in the liver McCrae considered liver involvement as common as that of the central nervous system It is at least third in frequency, with the aorta and central nervous system exceeding it The exact incidence of hepatic syphilis varies with the stage of the disease (early or late) and with different observers This variation is especially marked in early syphilis where the incidence

is greatly increased in patients who received heavy metal therapy. Thus Hahn in his excellent review of this problem diagnosed only five cases or 0.05% of early hepatic syphilis out of 10,000 before treatment. Waugh reports this incidence to be 0.08%. Others cite this frequency as 0.49 to 0.78% (Hahn) and 0.37% (Singer). Wile and Sams found jaundice in early untreated syphilis in 0.18% of cases but in 1.35% of treated cases. Soffer estimates that about 1% of treated syphilitics will exhibit jaundice. This marked increase of hepatic complications in early treated syphilis demands the conclusion that treatment in one way or another is responsible for them.

In late syphilis the true incidence of hepatic involvement may also be confused by inclusion of all cases of cirrhosis and the inclusion of mild, latent, or questionable changes. Thus Stokes gives a very high incidence, 10%. Moore reports 33 cases of hepatic syphilis among 8,500 necropsies in adults (0.38%) and 34 clinical diagnoses among 6,420 patients with late syphilis (0.53%). Hahn found the gross autopsy incidence to be 0.45% and 4.9% among 1,165 cases of adult syphilitics.

Pathology and Pathogenesis

Congenital Hepatic Syphilis

In congenital hepatic syphilis the liver is extensively invaded with spirochetes which apparently stimulate diffuse fibrosis. The outstanding feature in these livers is the marked increase in connective tissue between the columns of liver cells. There is a complete disorganization of hepatic architecture. Small gummata may be found scattered throughout the liver, and in the late benign congenital syphilis large gummas may result in a true hepar lobatum. This lesion is, however, more characteristic of acquired syphilis and will be described in greater detail below. Typical portal cirrhosis has been observed in patients showing the other stigmata of congenital syphilis, and here the question arises of the inter-relationship of the two processes. Rolleston and McNee postulate that congenital syphilis may make the liver more susceptible to other noxious agents with consequent development of cirrhosis.

Secondary Syphilis

Pathogenesis of jaundice in early (secondary) untreated syphilis most likely depends upon diffuse acute hepatitis produced by the spirochete. The widespread distribution of the organism makes its localization in the liver likely. However, since this lesion is rare and because of the lack of autopsy material, there is no certainty that these patients may not be afflicted with a viral hepatitis or other form of hepatic involvement. The demonstration of the spirochete in the liver and a distinctive morbid anatomy would help to elucidate this point. The use of needle liver biopsy in these cases may help to establish this entity more definitely. The pathologic findings available are in patients whose condition has progressed to acute yellow atrophy. Leonard found 59 cases (autopsied) of acute yellow atrophy reported in the literature and added one of her own. None of these patients received arsenical therapy but 12 of these were treated with mercury before onset of the disease. The pathology of these livers is not distinctive and resembles in every respect the acute yellow atrophy of infectious hepatitis. It is therefore not unreasonable to assume that a viral (infectious) hepatitis was superimposed on secondary syphilis. The predominant age incidence of 16–25 years is in agreement with the commonest age incidence of infectious hepatitis; however, early syphilis is also most likely to occur in this age group. The most important argument in favor of this hepatic involvement being of syphilitic origin is that most of these patients show a rapid disappearance of jaundice with arsenical therapy.

The *pathogenesis* of hepatic involvement in treated early syphilis introduces several other possibilities. The following factors have to be considered: (1) Herxheimer reaction, (2) infectious relapse, (3) arsenical (toxic) hepatitis, (4) infectious hepatitis and (5) homologous serum (syringe) hepatitis. While the first two are attractive explanations to syphilologists, they are applicable in a minority of cases. A Herxheimer reaction should occur very quickly within several days after the first injection of the arsenical, but this is rarely the case. In an infectious relapse one would expect the appearance of other lesions on the skin or mucous membranes, but this is also rare. While the arsenicals as well as mercury and possibly bismuth can have a hepatotoxic effect, one would expect to find a relationship between the amount of drug administered and hepatic involvement, but this is not the case (Soffer). Moreover, after administration of a toxin, evidence of hepatic involvement usually occurs very quickly, and further administration of the chemical results in further damage. Neither of these criteria is observed in post-arsphenamine hepatitis. Wile and Sams' group showed onset of jaundice 80 days after the last injection and the longest delay was 139 days. In Soffer's group 81 patients received further arsenical therapy, but in only two of these was there a recurrence of jaundice. These facts speak against a true arsenical hepatitis. This is more in keeping with a viral hepatitis transmitted by syringe, with its incubation period of 60 days or more. Furthermore, it was observed as long ago as 1920 by Stokes and co-workers that a tenfold increase of the incidence

of jaundice occurred in treated syphilitics without any other explanation except a coincidental increase of hepatitis in the general population This observation has been substantiated by others Not only the serum hepatitis but also the infectious hepatitis may be transmitted by syringe and the proper sterilization of needles and syringes would eliminate this type of jaundice (See Chapter on Viral Hepatitis p 256 and section on Toxic Hepatitis p 15)

The use of malaria as a therapeutic agent introduces another factor that is known to produce hepatic damage

Tertiary Syphilis (Gummas and hepar lobatum)

The pathologic unit of tertiary syphilis is a small granuloma or syphiloma The confluence of a large number of these microscopic granulomas results in the macroscopic gummas (Fig 36) Upon healing of the gummas deep contracted scars are formed which result in the bizarre lobulations to which the term hepar lobatum or botryoid liver (Fig 37a and b) has been applied

Although the liver is considered the commonest visceral site for gumma formation Symmers and Spain found it only 10 times in 23 792 autopsies in 30 years at Bellevue and Shapiro and Weiner found 79 cases in 21 years at Los Angeles General Hospital Only one lobe may be involved and according to McCrae the left lobe is more likely to be enlarged by a gummatous process The preponderance of the left sided enlargement has been denied by subsequent observers especially by Shapiro and Weiner The involved lobe may be the small and contracted one by virtue of scarification and the uninvolved lobe may be enlarged owing to hypertrophy The reverse is true if the liver is seen in the stage of the gummas The gummas may be seen as large firm rubbery masses resembling neoplasms Indeed isolated gummas have been mistaken for neoplasms and removed surgically Symmers and Spain found 7 solitary gummas in their 10 cases

While the liver is generally thought to be enlarged (Carter and Traut 90%) this has been denied by recent observers Thus the average weight in 53 livers was 1 556 gm or less than average (Symmers and Spain) The smallest of these weighed 608 gm and the largest 3 450 gm Hahn and Shapiro and Weiner agree that the liver is usually not enlarged Only three livers in the former series weighed more than 00 gm and nine livers in the latter series weighed over 1 800 gm

Marked thickening of Glisson s capsule has been noted and amyloid deposits in the liver have been reported In addition to the large scars the microscopic picture shows caseating tubercles with epi

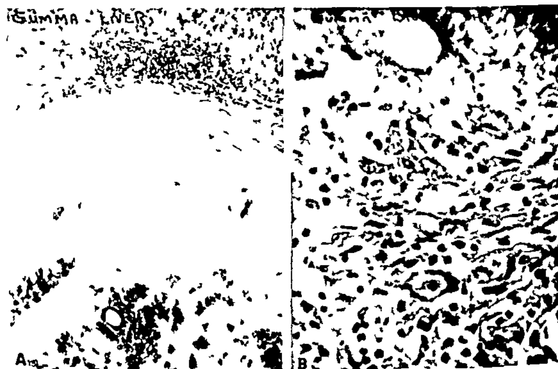


Fig 36 Gumma of liver A Low power shows the necrosis debris and the lymphocytic infiltration at periphery B Higher power shows giant cell in wall of gumma (Courtesy Dr Pirani Department of Pathology University of Illinois School of Medicine)

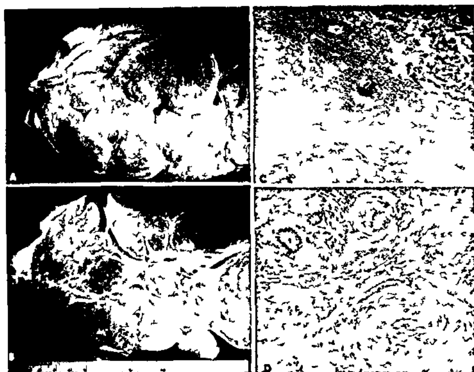


Fig. 37. Hepar lobatum (B y d l er).
A. View of surface of liver.
B. Cross section showing large scars d ce d g n o s b t ce of l r p od c g th b arre lobulation. Liver weight 2,250 gm.; spleen 80 gm.
C. × 70.
D. Microscopic section of scar in liver (× 140) showing b l d ct a d arteriole w h rrow g of l m thickening of wall and perivascular lymphocytic infiltration.
The patient was a 52-year-old Negro with diabetes and diabetic gangrene of s l toes. The liver was palpable fi ge bre d h below the costal margin. Total protein 5.7 gm/100 cc. Albumin 1.1 gm. Globulin 4.6 gm. Serum bilirubin 2 mg/100 cc. Total cholesterol 56 mg%. Esters 2%. Thymol turbidity 0.0. Flocculation o. Cephalin cholesterol flocculation 3 plus.

thelioid cells and syphilitic endarteritis (Fig. 37 C and D).

The spleen likewise varies in size and this variation is even greater than that of the liver. Symmers and Spain give figures for this organ of 60 to 1,980 gm. for adults but only 8 of 59 spleens reported by Hahn and 23 of 79 reported by Shapiro and Wiener weighed more than 300 gm. Symmers and Spain refer to distinctive changes in the spleen which consist of ochre-colored bodies composed microscopically of thickened and hyalinized arteries with mineralization of the muscular and elastic layers, perivenous hyaline deposits and periarterial hemorrhages.

With respect to other pathologic changes related to the liver and spleen, ascites was observed in 31% and esophageal varices in 15% in Symmers and Spain's series, while in Shapiro and Wiener's series the former was present in 5% of cases and the latter in 30%. The portal hypertension which is so common a finding in this disease and is responsible in part for the ascites and entirely for the esophageal varices is due chiefly to the contraction of the thick scars in the region of the porta hepatica obstructing the portal vein. The hepatic ducts are more successful in escaping this cicatrizing process; hence jaundice is less common and usually not marked.

Other syphilitic lesions are found in about two-thirds of autopsied cases. These lesions consist of syphilitic aortitis and central nervous system lesions most commonly. Less frequent lesions mentioned are fibrous orchitis, periostitis, focal syphilitic nephritis, chorioretinitis and gummas elsewhere in the body.

Cirrhosis

Syphilitic cirrhosis, one that can positively be identified histologically as such, is very rare in the

TABLE 38

Autopsy Incidence of Portal Cirrhosis in Adult Syphilitics as Compared with Adult Nonsyphilitics by Age

(January 1910 to February 1938 incl)

Age Group	Number of Nonsyphilitics	Number with Portal Cirrhosis	Per cent with Portal Cirrhosis	Number of Syphilitics	Number with Portal Cirrhosis	Per cent with Portal Cirrhosis
20 to 29	716	3	0 4	161	0	0 0
30 to 39	8 1	8	1 0	304	6	2 0
40 to 49	946	9	3 1	307	19	6
50 to 59	855	30	3 5	250	13	5
60 to 69	707	4	3 4	99	5	5 1
Over 70	415	8	1 9	34	1	9
Not determined	45	—		10	—	
Total	4 505	10	2 3	1 165	44	3 8

R D Hahn Syphilis of the Liver Am J of Syph Gon & Ven Dis 7 5 9 1943

acquired disease The diffuse fibrosis is the result of numerous miliary syphilomas which on healing produce the diffuse fibrosis In all of the 247 autopsied cases reported by Hahn Symmers and Spain and Shapiro and Weiner not one such lesion was found Another phase of the problem is whether syphilis is a contributory factor in the pathogenesis of portal cirrhosis from a statistical point of view this seems to be the case A history of syphilis positive serology or other evidence of syphilis is more commonly found in cirrhotics than in the rest of the population This fact has been pointed out by numerous observers (see Chapter 5) Schumacher found presumptive evidence of syphilis in 8 8% of 45 cases (autopsied) of portal cirrhosis while a similar noncirrhotic group showed the incidence of syphilis to be only 4 4% Approaching this problem from another point of view Hahn found portal cirrhosis in 3 8% of 1 165 adult syphilitics and only 3% cirrhosis in 4 505 adults without syphilis (see Table 38) In other words cirrhosis is commoner in syphilitics and syphilis is more commonly seen in portal cirrhosis

The significance of this relationship is speculative The following possibilities exist (1) Syphilis itself contributes to liver damage (2) Therapeutic agents used contribute to liver damage (3) Habits and environmental factors of these individuals promote both conditions

In regard to the first point it is very tempting to assume that during the stage of spirochetosis with fever and evidence of systemic infection the liver does become involved During the long clinical cycle of the disease some insiduous and clinically undetectable pathologic changes in the liver may be going on Stoke s latent hepatic syphilis idea favors this viewpoint The lack of distinctive pathologic imprint is against this theory but is not necessarily crucial for we know that the liver may respond similarly to a variety of noxious agents

The second point the toxic agents that have in the past been used therapeutically cannot be dismissed lightly No one denies the toxicity of these agents A study correlating the amount of these agents used with the final hepatic picture would do much to clarify the role of the heavy metals I have been unable to find accurate information on this point In Hahn s series some of the patients with cirrhosis and syphilis did receive adequate antisyphilitic therapy and therefore considerable amounts of toxic drugs However one would not expect a straight line relationship for the more heavy metal used the more adequate the antisyphilitic therapy the less the noxious influence of the Treponema on the liver Also the variable individual reaction to a given toxin makes it difficult to assess its proper effect in a given case

The third important point encompasses the habits environmental and nutritional factors of these individuals History of alcoholic excesses is commoner in individuals with syphilis than in the control group A frequent concomitant of alcoholism is that of poor nutritional habits It should not strain one s credulity to suggest that individuals prone to acquire syphilis are more careless about their personal habits and hygiene than their nonsyphilitic brethren In summary we may say that all three of the above factors may play a role in the genesis of cirrhosis in syphilis The exact importance of each factor undoubtedly varies but syphilis itself is the least important of the three with heavy metal therapy greater and nutritional habits of greatest importance The displacement of heavy metal therapy with penicillin may help to clarify its importance in the future studies

Syphilis of the Liver—Summary

Incidence of liver involvement

Early (untreated) syphilis 0 03% to 0 78%

Early treated syphilis 1 35%

Late (tertiary) syphilis

Among all autopsies 0 45%

Autopsies of adult syphilitics (Hahn) 4.9%

Pathology and Pathogenesis
- Congenital hepatic syphilis
  - Diffuse fibrosis between cords of liver cells
  - Numerous small gummata
  - Disorganization of architecture
- Secondary (early) hepatic syphilis (untreated)—very rare
  - Spirochetal hepatitis (?)
  - (Is it viral hepatitis?)
- Secondary (early) hepatic syphilis (treated)
  - Pathology similar to viral or toxic hepatitis.
  - Is it caused by one of the following?
    - (1) Herxheimer reaction
    - (2) Infectious relapse
    - (3) Arsenical hepatitis
    - (4) Infectious hepatitis
    - (5) Homologous serum hepatitis
- Tertiary syphilis
  - Syphiloma—confluent produces
  - Gummas—these heal with large deep scars producing
  - Hepar lobatum
  - Size—may be smaller than normal—608 to 3,450 gm
  - Only one lobe may be involved
    - Left lobe may be more commonly enlarged (McCrae)
    - Enlarged lobe may be one involved by gummas
    - Enlarged lobe may be the uninvolved hypertrophied lobe
  - Spleen may also be enlarged, occasionally enormous (1,980 gm.)
  - Ascites
  - Esophageal varices
  - Associated pathology
    - Syphilitic aortitis
    - CNS syphilis
- Syphilitic cirrhosis
  - Rare in tertiary syphilis
  - Portal cirrhosis more common in syphilis
    - Cause?
    - 1. Spirochete
    - 2. Hepatoxic drugs
    - 3. Greater frequency of alcoholism and malnutrition

Clinical Picture

Age

The early syphilitic involvement of the liver occurs in young persons 16-25 years of age. Tertiary syphilis of the liver occurs later in life with an average age around 40. The age range is 19-90 (see Table 39).

Sex

The sex shows a preponderance of males—2:1 or more. The predilection of this form of syphilis among the white race is surprising in view of the greater frequency of syphilis among Negroes.

Symptoms

The symptoms vary greatly and are not diagnostic. The presenting complaint is frequently upper abdominal distention and discomfort. Pain may be dull, aching or gnawing in nature and accompanied by anorexia, nausea, distention and vomiting. Occasionally the pain may be quite severe and suggest cholecystitis. This is especially true since its location is commonly the right upper abdominal quadrant. Pain may be referred to the right side of the chest and be pleuritic in nature, suggesting pulmonary pathology. Weight loss may be a conspicuous feature. Hematemesis and tarry stools from bleeding esophageal varices are serious symptoms and occur in about one fourth of these patients. Changes in bowel habits are occasionally noted. Chills and fever may be a conspicuous feature and suggest an acute infection. A previous history of jaundice is sometimes elicited.

Physical Findings

The patient may give the picture of an individual both acutely and chronically ill. The temperature may be 103° or higher and show a tendency to morning remissions. A febrile course is frequent: it was noted in 1- of Hahn's 77 cases, in 1- of 28 cases by Symmers and Spain, and in both cases recently reported by Tucker and Dexter. The importance of fever as a symptom is minimized by Shapiro

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acquired disease The diffuse fibrosis is the result of numerous miliary syphilomas which on healing produce the diffuse fibrosis. In the 4 autopsied cases reported by Hahn, Turner and Spain and Shapiro and Weiner no organisms were found.

Another phase of the problem is whether syphilis is a contributory factor in the pathogenesis of portal cirrhosis. From a statistical point of view this seems to be the case. A history of syphilis, positive serology or other evidence of syphilis is more commonly found in cirrhotics than in the rest of the population. This fact has been pointed out by numerous observers (see Chapter 5). Schumacher found presumptive evidence of syphilis in 8 8% of 4 cases (autopsied) of portal cirrhosis while a similar noncirrhotic group showed the incidence of syphilis to be only 4 4%. Approaching this problem from another point of view Hahn found portal cirrhosis in 3 8% of 1 165 adult syphilitics and only 3% cirrhosis in 4 505 adults without syphilis (see Table 38). In other words cirrhosis is commoner in syphilitics and syphilis is more commonly seen in portal cirrhosis.

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TABLE 39

Summary of Clinical Signs and Symptoms of Tertiary Hepatic Syphilis

	McC	Hah	Sh p & W	Symm s & Sp
Number of cases	100	73	79	8
Number of autopsies	0	66	79	8
Age range	1–70 yrs	0–70 yrs	–90 yrs	19 80 yrs
Highest age incidence	31 40 yrs	equally distributed	61–70 yrs	30–50 yrs
Sex	66 M 34 F	41 M 16 F	43 M 36 F	3 M 5 F
Ratio White colored	70 W 30 C	17 W 40 C	64 W 15 C	4 W 4 C
Chronic use of alcohol	55%	?	15%	1%
Fever	81%	16%	1 3%	43%
Jaundice	40%	1 %	16%	28%
Hematemesis	10%	1 5%	5%	5%
Ascites	4 %	11%	5%	64%
Palpable liver	89%	30%	46%	64%
Enlarged left lobe of liver	49%	?	0%	
Lumpy liver	9%	1 %	0%	1%
Palpable spleen	50%	14%	11%	44%
Other syphilitic lesions	?	61%	39%	
Vascular spiders	?	0%	1 3%	
Positive serologic tests	80%	81%	88%	
Coincidental portal cirrhosis	?	1 5%	6 3%	

Modified from Shapiro and Weiner The Diagnosis of Tertiary Syphilis of the Liver Twenty Five Years After McCrae Am J Med Sc 494 1951

and Weiner (1 3% of their cases) The fever depends on absorption of necrotic material from gummas Dehydration may accompany the fever *Jaundice* may be present in 10–30% of cases The jaundice is usually not intense Liver enlargement is no longer considered an important clinical finding Hepatic enlargement may however be commoner clinically than at autopsy (see Pathology) This may depend on the stage and evolution of the process Clinically one more frequently sees the patient while gummas are prominent but by the time the patient reaches the autopsy table the gummas may be replaced by scars and the liver shrunken The liver is palpable about half of the patients but marked en may be present in only a fraction of The liver may also be tender The largement may be confined to one lobe and coarse nodularity or a single large mass may be found This results in confusion with neoplasm Upward enlargement of the liver may result in elevation of the right side of the diaphragm this is rare since unilobular enlargement is more frequent in the left lobe A friction rub over the liver may be present because of the perihepatitis

The spleen may be palpable less frequently than the liver Occasionally the spleen is enormously enlarged and with bleeding esophageal varices has earned the term Banti s syndrome Ascites is not an infrequent finding along with the splenomegaly and esophageal varices it is related to cicatricial obstruction of the portal vein Dilated superficial veins are occasionally seen The rarity of spider naevi is emphasized by Shapiro and Weiner Along with ascites peripheral edema may be present

Other evidence of syphilis may be found and should be looked for aortitis aortic insufficiency or aneurysm are most frequently found Central nervous system syphilis tabes and general paresis may be evident Gayle and Quisenberry reported an interesting case of general paresis in which jaundice and ascites developed after malarial therapy The stigmata of congenital syphilis and gummata elsewhere should be searched for

LABORATORY FINDINGS

The serologic test for syphilis is almost always positive but it may be negative in 10% of cases The blood in addition shows a microcytic anemia and normal or low white count

The anemia has been noted in patients who showed no evidence of blood loss

The total plasma proteins may be normal low or elevated but the globulins are usually elevated and therefore the A/G ratio is decreased Occasionally the flocculation tests especially the cephalin cholesterol flocculation is positive The alkaline phosphatase is frequently elevated even in the absence of jaundice The B S I test is usually normal or shows only slight retention The prothrombin time the cholesterol partition and hippuric acid tests may give normal values The urine contains bilirubin and urobilinogen when jaundice is present

Diagnosis and Differential Diagnosis

The diagnosis should be strongly suspected when a patient with known syphilis develops hepatic enlargement nodularity pain fever jaundice ascites and elevated alkaline phosphatase In practice however a correct antemortem diagnosis is rarely made In only 3 of 28 case reviewed by Symmers and Spain in 4 of 77 cases of Hahn and in 5 of 79 cases of Shapiro and Weiner was the clinical diagnosis made Two of these were diagnosed by peritoneoscopy and at laparotomy The rarity of a correct clinical diagnosis partly reflects the low index of suspicion of this entity In patients with syphilis the development of ascites or other signs of liver disease should at least arouse the suspicion of hepatic syphilis If the ascites is unaccompanied by strongly abnormal liver function tests and there is an absence of spider naevi the suspicion of hepatic syphilis should be heightened Needle biopsy should help to clarify the diagno i However the finding of a caseating granuloma may still not rule out other granuloma

Tertiary hepatic syphilis may have to be differentiated from the following groups of diseases depending upon the clinical picture (1) Liver abscess if chills and fever dominate the picture—leukopenia should help to rule this out (2) Cholecystitis and cholelithiasis if pain fever and jaundice predominate The greater frequency of syphilis in the male nodular enlarged liver leukopenia and changes in pla ma protein will direct one to the liver instead of the biliary tract (3) Hepatic neoplasm is the most frequent diagnostic error in solitary gummas and biopsy may be needed to dispel the confusion however the rapid downhill course of primary carcinoma and the evidence of a primary ource in metastatic neoplasms may help here In benign neoplasms the patient does not look ill and the clinical picture is not progressive (4) Cirrhosis of the liver as a rule shows more abnormality in liver function tests spider naevi and palmar erythema are frequently found (5) Other conditions that may require differentiation are other granulomas cysts of the liver subphrenic abscess renal disease and other intra abdominal abscesses or tumors

Prognosis

Hahn estimates that in only 6 of 1 000 cases of syphilis is the involvement of this organ a contributory factor in the patients death That this condition is compatible with longevity is seen from the fact that some of these patients exceed the average life span With the development of ascites portal obstruction and esophageal varices death may occur from esophageal hemorrhage (5%) or cholemia (8 9% Shapiro and Weiner) The finding at autopsy of shrunken livers indicates the degree to which the liver can atrophy however if the diagnosis is not delayed too long adequate therapy should save the patient or considerably prolong his life

Treatment

Adequate treatment of early syphilis would effectively prevent hepatic involvement The prolonged debate whether arsenicals should be used in the treatment of hepatic syphilis is at present merely academic since penicillin is the drug of choice Arsenic has been used w th good results in early hepatic syphilis and its cautious use is permissible in late syphilis after the use of bismuth and iodides The therapeutic paradox of improvement of the syphilis but progressive liver failure was attributed to rapid scarring of liver after the gummas had healed

Penicillin in a dosage of 40 000 units every

three hours for ten days was found very effective by Tucker and Dexter A response was seen to smaller doses as well Clinical improvement was prompt, abnormal laboratory findings changed to normal The decrease of liver size is gradual and return to normal may take several years Procaine penicillin would probably be just as effective and less cumbersome to use Penicillin may be used without danger even in the presence of cardiovascular syphilis

29 Relapsing Fever

RELAPSING fever is an acute infectious disease caused by a spirochete of the genus Borrelia transmitted by a tick or louse and characterized clinically by chills high fever and muscular aches terminating in crisis followed by several relapses Its synonyms are Typhus *recurrens* tick *fever* kimputu

ETIOLOGY

Vectors and geographical distribution

The disease is generally divided into two groups depending upon the vector that transmits it to the human host namely the louse borne variety and the tick borne variety These are then subdivided into their geographical distribution The louse borne is more important in Central and Eastern Europe as well as in the Orient the tick borne disease is most important in the United States but also occurs in Spain Greece the Near East Asia and Africa

The louse borne disease is transmitted by Pediculus humanus and can be prevented by improved sanitation The spirochete is transmitted not by the bite of the insect but by crushing the insect and rubbing its contents into the abraded skin The American Army Medical Department had experience with this disease in the Chinese Theatre (Wolff) After World War I over 1 5 million cases occurred in Eastern Europe in epidemic form

The tick borne disease is transmitted by the bite of a tick of the species Ornithodoras This species of tick and the disease that it carries has been reported from California Nevada and Texas In the West and the Rocky Mountains O hermesi and in Texas O turicata are the ticks incriminated In the tick borne disease rodents are the source of infection In the United States the disease is rare but should be reckoned with in the regions mentioned In California 69 cases were reported from 1921 to 1934 (Wynn and Beck) and in Texas 258 cases in a five year period (Kemp and associates)

The Organism

The spirochetes that cause this disease are similar morphologically but immunologically separated into several subgroups Borrelia recurrentis is transmitted by the louse B novyi (Texas) and B duttonii are among the more important of the species transmitted by the tick This spirochete is 10 to 16 microns in length and has 4 to 10 loose coils which are tapered at both ends

Epidemiology

The louse borne disease is commonest during war famine or any disaster that results in a break down of sanitation It is commonest in winter when exposure to the louse is most likely The tick borne disease is commonest in summer and in rural communities where exposure to the tick is most likely

Sex

Males are the most commonly affected in both types because of their greater opportunity for exposure

Age

It is rare in children under five and has been reported in individuals over 70

PATHOLOGY

Jaundice and hemorrhages are often found in the fatal cases The hemorrhagic phenomena may be found in both the skin and internal organs The liver is enlarged and may show cloudy swelling and fatty degeneration Fatty changes are seen in the heart and kidneys as well The spleen is enlarged and may show infarctions Perivascular infiltrations and petechial hemorrhages have been noted in the brain

CLINICAL FEATURES

The clinical features vary somewhat with the type of disease and the condition of the patient The louse borne disease is usually more severe and carries a higher mortality but it also occurs most frequently in persons who are debilitated by other diseases or by malnutrition

The incubation period is 7 to 15 days in the tick borne disease and slightly shorter in the louse borne disease

The onset is usually abrupt but there may be some prodromal malaise The disease is ushered in with a chill and the temperature rises to 103 to 104 or higher The fever is frequently accompanied by headache vomiting and muscular aches Pulmonary symptoms may be present Epistaxis hematemesis and melena may occur The sensorium is usually clear but delirium may be present

The physical examination reveals an acutely ill patient The conjunctivae may be injected Erythematous petechial or purpuric rashes have been observed The severely ill patients have jaundice and this may be very deep The icterus is probably due to hepatocellular damage (spirochetal hepatitis) although increased bilirubin production from tissue hemorrhages may play a role The jaundice may persist for 10 to 0 days after clinical recovery Fifteen of the 134 patients reported by Wolff were icteric Transient rales may be heard in the lungs The heart shows a tachycardia which is in keeping with the fever The liver may be enlarged and tender but is soft in consistency Hepatomegaly was demonstrated in 2 of Wolff s cases The spleen is more frequently enlarged Signs of encephalomeningitis such as loss or diminution of reflexes and poorly reacting pupils are occasionally seen

Defervescence occurs by crisis after about three days of continuous fever This is accompanied by drenching sweats and followed by asthenia Severely ill and debilitated patients may go into peripheral vascular collapse shock and death may ensue In the usual case the patient begins to feel well The afebrile period may last from several days to a week when a relapse occurs The relapses are accompanied by milder symptoms but occasionally they may be more violent than the original attack

COMPLICATIONS AND SEQUELAE

Sequelae of nephritis iritis cranial nerve palsies and meningitis have been reported In cases accompanied by nephritis and meningitis relapsing fever may be mistaken for Weil s disease Mild myelitis orchitis and parotitis have been observed as complications

LABORATORY FINDINGS

Moderate leukocytosis with a preponderance of polymorphonuclear cells is usually found

The urine in addition to traces of albumin contains bilirubin and urobilinogen in the icteric cases Liver function studies are not reported in this disease but an increased gamma globulin and positive flocculation tests are to be expected

Bacteriological and serological studies are of utmost diagnostic importance The spirochete can be found in the blood by direct smear in the early febrile state or during relapses Their abundance depends on the severity of the disease they are difficult to find after the crisis or during the afebrile remissions Thick or thin blood smears may be stained as for the malarial parasite with Wright s Giemsa or gentian violet stain During the afebrile period the organism may be recovered from the blood by inoculation into white mice Clotted blood

may be shipped to laboratory since the organism remains viable for about six days Because the above test may fail or be inconclusive Stein suggested an agglutination and complement fixation test with the use of washed spirochetes derived from saponin hemolyzed infected mouse blood This antigen gave positive results with various strains of spirochete of relapsing fever but negative in syphilis Weil s disease typhoid and other infections Positive serological tests for syphilis are frequently obtained in this disease but in the absence of syphilis disappear during convalescence

Diagnosis

The diagnosis depends on the typical fever with remission and relapse the leukocytosis tachycardia and the finding of the specific organism or positive serological tests It has to be differentiated from malaria typhoid typhus influenza Weil s disease and other infections Usually the differentiation can be made on the basis of the typical fever and other clinical features if the disease is thought of The diagnosis can be clinched by the bacteriological or immunological tests While uncommon in this country it should be thought of in the several states mentioned

Treatment and Prognosis

The *arsenicals* neoarsphenamine and Mapharsen have been used with excellent results One or two injections usually suffice Neoarsphenamine in doses of 0 45 and 0 6 gm on alternate days may be sufficient Mapharsen 0 04 gm in two doses 3 to 5 days apart has been found effective Arsenicals are thought to be dangerous in patients with severe jaundice and at the time of crisis If the patient is seen during the crisi the arsenicals should be administered during the next relapse

Penicillin has been found effective against experimental infection with B recurrentis as well as in clinical cases Crystalline penicillin G has been found most effective against this organism A dose of 30 000 units every three hours intramuscularly is effective and does not have the drawbacks of the arsenicals It has been found effective when the arsenicals failed

Relapsing Fever—Summary

Etiology
- **Vectors**
  - **1 Louse (Pediculus humanus)**
  - **2 Tick (Ornithodoras)**
- **Organism**
  - **Spirochete**
    - **Borrelia recurrentis (louse borne)**
    - **B novyi, B duttonii (tick borne)**
- **Geographical**
  - **Louse borne commonest in Orient and Eastern Europe**
  - **Tick borne found in U S A but also in Mediterranean Near and Far East**

Pathology
- **Jaundice and hemorrhages**
- **Liver enlarged and shows cloudy swelling also fatty degeneration**
- **Heart and kidney—fatty changes**

Clinical Features
- **Vary with type of disease severe in louse borne variety**
- **Incubation period 7 to 15 days**
- **Onset abrupt**
  - **Temperature 103 to 104 headache vomiting malaise muscular aches epistaxis hematemesis**
- **Findings**
  - **Conjunctivae injected**
  - **Rash—erythematous petechial or purpuric**
  - **Jaundice—severely ill patient**
  - **Liver enlarged soft and tender in 15 to 20% of cases**
  - **Spleen more commonly enlarged**
- **Defervescence by crisis after three days—peripheral collapse and death may occur**
- **Afebrile period—3 to 7 days**
- **Relapse usually not as severe as original attack**

Diagnosis
- **Febrile state**
  - **Spirochete found in blood**

Thick or thin blood smear stained with Wright's stain, Giemsa's stain or gentian violet

Afebrile period

- Spirochete can be found by inoculation into white mice
- Agglutination
- Complement fixation tests

Treatment

- Neoarsphenamine 0.45 to 0.6 gm on alternate days
- Mapharsen 0.04 gm two doses 3 to 5 days apart
- Arsenicals dangerous in severe icterus
- Penicillin G 30,000 units every three hours

30 Weil's Disease

WEIL'S disease is a specific infectious disease caused by *Leptospira icterohaemorrhagiae*. It is characterized clinically by sudden onset of fever, headache, vomiting, muscular pains and tenderness, followed by hemorrhages, azotemia and jaundice; and pathologically by hepatic, renal, capillary and skeletal muscle damage.

It is also known as spirochetal jaundice, leptospiral jaundice, epidemic jaundice, infectious jaundice, typhus bilieux, spirochetosis icterohaemorrhagica.

While usually the use of a proper name in the nomenclature of a disease is to be avoided, this disease is perhaps an exception to the general rule. Weil's disease is a short, easily remembered term, firmly entrenched in the literature, referring to infection by the specific spirochete, and dates back to the original description of this disease by Weil in 1886. The other term which has the virtue of accuracy—but is rather long and clumsy—is spirochetosis icterohaemorrhagica. Other terms are best avoided because they lack accuracy and specificity and are confusing. All terms that include the word "jaundice" are inaccurate since jaundice does not develop in all patients. The terms "spirochetal" and "leptospiral" are nonspecific since there is an entire group of different organisms that may cause similar but not identical clinical pictures. Epidemic jaundice and infectious jaundice may be confused with infectious (viral) hepatitis.

Etiology

Bacteriology

The *Leptospira icterohaemorrhagiae* was first described by Noguchi in 1918, who erroneously thought it to be the cause of yellow fever. It varies in size, with an average length of [illegible] 14 microns (up to 40 microns) and 0.[illegible] microns in diameter. The spirals are uniform and run through its entire length, and it is slightly hooked at each end. It is actively motile, and propulsion occurs by rotary motion of its hooked end. When in motion it seems to be drawn out into a straight line except for the hooked end. It grows well on Noguchi's leptospira media at temperatures from 25 to 30° C.

It should be pointed out that other leptospira can produce infections in man, and some of these are clinically similar to Weil's disease. At least sixteen other species have been described. While studies in the United States have been confined to *L. icterohaemorrhagiae*

TABLE 40

Some Leptospira Pathogenic to Man

Lepi p	D M	A mal R rr	G g ph l D i b tio
L icterohaemorrhagiae	Weil s Disease	Rattus Norvegicus	World Wide
L grippotyphosa	Swamp Fever	Species of Mice	Europe N E I †
L sejroe	Swamp Fever Infectious Jaundice	Rats	Denmark Italy
L canicola	Canicola Fever	Dogs	World Wide
L hebdomadis	Japanese Seven Day Fever	Mice	Japan
L bataviae	Infectious Jaundice	Rats Mice	N E I Japan Italy
L pomona	Infectious Jaundice Swine hea d s Disease	Rats	Australia Italy Switzerland

Recently reported from Texas (Coffey Dravin & Dine) From Editorial Ann Int Med *33* 481 1950
† Recently reported from Texas (Spain & Howard)

and L canicola there is reason to believe that other species are found in this country L pomona and L grippotyphosa infections have been reported in the United States (Coffey et al Spain and Howard) The different varieties can be separated by immunological methods which are dependent upon antigenetic differences

L canicola is the other leptospira of some significance in this country Several recent reports have served to emphasize its importance in this country (Gordon 195- Haunz et al 195- Beeson and Hankey 1952) It produces a mild febrile illness which is referred to as canicola fever The animal reservoir is the dog Some of the other more exotic leptospiral diseases should be mentioned here because they all have a sudden onset with fever malaise and myalgias and are often accompanied by hepatic involvement Table 40 shows some of the leptospira pathogenic for man and their predominant geographical distribution

Epidemiology

The *vectors* for most of these infections are rodents The rats that carry the L ictero haemorrhagiae are heavily infected in the United States and surveys show that 7–60% of rats examined are carriers of this leptospira The renal lesions in these animals result in excretion of the organism in the urine—a situation which may continue throughout the life of the animal In addition to rats the organism has been found in mice dogs cats pigs foxes and horses The organism gains entrance into the human host through abrasions in the skin or mucous membranes when contact is by immersion in polluted water The leptospira may be ingested with food or water contaminated by infected excreta, or may be direct by a bite from the infected animal

Man to man transmission is apparently rare in spite of the fact that the organism is excreted in the urine during a period of the disease However a case of transmission via copulation and a case of intrauterine infection of the fetus have been reported

Occupation

Since exposure to rats or rat excreta is the most frequent source of infection the disease is most frequent in individuals exposed to such contacts Such occupations include stockyard workers fish workers plumbers garbage collectors miners farmers and wharfmen Miners in England show the highest occupational rate of infection (Gardner and Wylie) (Table 41) Swimming or accidental immersion in pol

TABLE 41

Prevalence of Weil s Disease in Certain Occupations

O p t	Numb of C
Colliers (miners)	7 (18 0%)
Farm workers	13 (8 6%)
Bathing and accidental immersion	1 (8 0%)
Sewermen	6 (4 0%)
Butchers	5 (3 3%)
Fish workers	(1 3%)
Male Army personnel	13 (8 6%)
A T S	(1 3%)
Naval personnel	4 (7%)
R A F	3 (0%)
Italian prisoners-of war	5 (3 3%)
Miscellaneous or unknown	45 (30 %)
Total	137

From Gardner and Wylie Lancet *1* 955 1946

luted streams is a common means of infection In Holland the canals are a common source of infection and account for the high incidence of the disease in that country The occupational nature of the disease has received legal recognition It is regarded as a compensable occupational disease in fish workers in New York and in some occupations in England

Sex

Because of the occupational hazards involved Weil s disease is much commoner in males 90% of the cases in this country have occurred in males This sex preponderance is true in other countries and is due purely to incidence of contact and not to difference in immunity It has been pointed out that among a group of fish workers most of whom were women the disease was three times commoner in this sex L canicola infection is also commoner among women for they more frequently care for sick dogs—the source of the infective agent

Age

The disease is rare in young infants and children although it is known to occur in the early period of life Intrauterine infection has been reported Walch Sorgdrager found that 210 of 370 cases occurred in the age group of 10-40 and the frequency declined at both extremes of life

Seasonal Incidence

The majority of cases have occurred in this country during June July August and September Similar seasonal distribution has been reported in Europe The summer rise may be in part attributable to more frequent bathing swimming and wading in polluted water The disease does occur all year round In England a rise in February and March has been noted on an occupational basis (Gardner and Wylie)

Geographical Distribution

The disease is truly ubiquitous It has been reported in 46 countries and all five continents (Walch Sorgdrager) In Europe it is present as far south as Italy and as far north as Sweden In America it stretches from Argentina north to Canada In the United States it has been considered a rare disease Up to 1941 Ashe and co workers found only 67 reported cases including their own In the decade since then the disease has been reported much more frequently in this country 78 cases of leptospiral infections were reported from the Detroit area (Molner et al) Patterson estimates that 300 cases have been reported This is due partly to the increased awareness of the disease which was stimulated by the excellent reports and reviews in the American literature and partly to the increased utilization of specific diagnostic (bacteriological and immunological) procedures Failure to recognize its esoteric form in the United States also accounts for the small number reported However the higher level of sanitation and pest control may account for the lower incidence In Holland 808 cases were reported to the public health service between 19 9 and 1939 (Walch Sorgdrager) 182 positive erological tests for Weil s disease were reported from 1940 to 1945 by a laboratory in England (Gardner and Wylie) Sixteen per cent of all the human sera examined were positive

Etiology—Summary

Organism—spirochete
Leptospira icterohaemorrhagiae
Vector—rodents (rats mice dogs cats pigs foxes and horses) contact with excreta or bites
Occupation (frequent contact with above) stockyard fish workers farmers miners plumbers garbage collectors
Sex—Males predominate
Age—10-40 less frequent at either extreme of life
Season—summer
Geographic distribution—all five continents reported from 46 countries

PATHOLOGY

The outstanding feature of the morbid anatomy of this disease is the preponderant damage of the following structures liver kidney capillaries skeletal muscles

1 *The lesions of the liver* are most important from the point of view of the present thesis but not necessarily the most important lesion in this disease This organ may appear normal on gross inspection but is usually bile stained and frequently slightly

enlarged It is never shrunken as in acute yellow atrophy Obstruction of extrahepatic bile ducts is not seen in this disease Mucous plugs of the common bile ducts are mentioned once in the literature

Microscopically the following features are noted (a) proliferation of hepatic cells (b) degeneration and necrosis of parenchymal cells and (c) biliary stasis The proliferation manifests itself by binucleated or multinucleated cells While most of the cell division is amitotic mitotic figures are seen Since the regenerative ability of the liver is very high and evidence of regeneration may be seen even in the normal liver these features cannot be considered distinctive for Weil s disease The degenerative features consist of cloudy swelling vacuolation of cells as well as pyknosis karyolysis and swelling of nuclei Fatty infiltration is either absent or very slight Necrosis of varying degree is seen but this is usually slight and focal However necrosis may be so extensive as to simulate yellow atrophy (the liver is not diminished in size however) Central zone necrosis was reported by Ashe et al in two of their cases Biliary stasis is noted in the central portion of lobules This may consist of granules of bile in the swollen cell cytoplasm and the central bile capillaries Rupture of bile capillaries with resultant leakage of bile into sinusoids may occur There is no evidence of biliary stasis in the periphery of lobules or in the large bile duct

Other changes consist of an exudative process with periportal infiltration of lymphocytes polymorphonuclear leucocytes and eosinophils Small portal and subcapsular hemorrhages are seen and more rarely scattered hemorrhages throughout the liver occur Spirochetes may occasionally be demonstrated in perisinusoidal lymph spaces Kupffer cells may show occasional fat droplets While the liver lesions are not diagnostic morphologically they are most likely due to the toxic effect of the spirochete

The kidneys are usually enlarged and show the greenish brown color of jaundice Small subcapsular hemorrhages may be seen grossly Microscopically edema and necrosis of epithelium of the convoluted tubules and the interstitial inflammatory process are the outstanding features The glomeruli usually escape damage but o casional change n Bowman s capsule and the glomerular tuft may be difficult to differentiate from acute glomerulonephritis The tubular changes predominate and consist of the entire spectrum from cloudy swelling to actual necrosis The edema of the tubular epithelium and the collective desquamated cellular debris within the lumen undoubtedly play an important role in the production of azotemia and renal failure These renal changes are more likely due to the toxic effect of the spirochete rather than damage from bile This viewpoint is favored by the fact that some degree of azotemia may be present without jaundice In the interstitial tissue and in the lumen of the tubules the spirochetes may be demonstrated

3 The capillary damage is one of the conspicuous features of the disease which owes its name to this characteristic The damage to these vessels results in diffuse hemorrhages which may be minute and inconspicuous or large confluent and very obvious These hemorrhages are generally distributed throughout the body but are commonest under serosal surfaces (peritoneum and pleura) the gastrointestinal tract kidney nasal mucosa adrenals and skin The adrenal hemorrhages have not been reported to result in clinical evidence of insufficiency They have been noted beneath the endocardium and pericardium in the mesentery spleen pancreas and bladder Hemorrhages in the liver and kidneys have been mentioned previously

Hemorrhages in the trachea bronchi and lungs may produce a picture of hemorrhagic pneumonia Hemorrhages in brain and meninges have been described The pulmonary and central nervous system hemorrhages may be important as a cause of death Peripheral nerves may also be the site of hemorrhage The capillary lesions are probably due to the toxic effect of the spirochete on their endothelium

4 Skeletal muscles show a pathognomonic lesion most readily demonstrated in the gastrocnemius Other muscles are similarly but less extensively involved The importance of this lesion was emphasized by Jeghers et al and more recently by Sheldon (1945) who proposed muscle biopsy for diagnostic purposes In the biopsy material it was noted that the number and extent of the muscle lesions varied with the severity of the disease But this variation was quantitative while qualitatively the lesions were identical The earliest changes consist of the appearance of small and medium sized vacuoles within the cytoplasm of striated muscle fibers These vacuoles become confluent Simultaneously the muscle fiber loses its cellular detail The longitudinal fibrils and cross striations disappear and irregular masses of acidophilic material remain Infiltration with histiocytes polymorphonuclear leucocytes and plasma cells also takes place Reabsorption and proliferation of nuclei of sarcolemma have been noted as well as hemorrhages into empty muscle sheath (Jeghers et al) Sheldon found these typical lesions in all of sixteen biopsies in seven patients with Weil s disease They are considered to be distinct from such lesions as Zenker s necrosis

Lesions in other organs are found but are not as constant as the ones described above Spirochetes may be found in every organ of the body Following is the order of frequency kidney liver adrenals myocardium intestinal wall appendix pa creas prostate lung spleen lymph nodes skeletal muscle and the wall of the urinary bladder The lungs may show hemorrhagic pneumonia The heart may be normal but myocarditis may be present as evidenced by cellular infiltration perivascular and interstitial Degeneration of myocardium may resemble the changes in the skeletal muscles Vegeta

tive endocarditis with spirochetes demonstrated in the vegetations has been reported The hemorrhagic lesions in the gastrointestinal tract have been mentioned This has resulted in colitis and necrosis of the large bowel Meningeal inflammation is found but is not as important from the pathological point of view as it is clinically Leptospiral meningitis is usually not fatal however The spirochete has been found in the meninges and their infiltration with macrophages is referred to by Walch Sorgdrager

Pathology—Summary

1 Liver grossly bile stained enlarged moderately
   Microscopically
      Proliferation } of parenchymal cells
      Degeneration }
      Necrosis—focal (centrolobular)
      Biliary stasis (centrolobular)
      Exudative process (periportal)
      Hemorrhages—subcapsular
2 Kidneys grossly enlarged greenish brown color subcapsular hemorrhages
   Microscopically
      Edema } convoluted tubules
      Necrosis }
      Desquamated debris in lumen
3 Capillary damage—results in
      Hemorrhages—petechial and ecchymotic
      Serosal surfaces gastrointestinal tract skin mucous membranes
4 Skeletal muscles especially calf
      Vacuoles—confluence striations disappear mass of acidophilic material

Clinical Features

The incubation period has been given by Inada as five to seven days Opportunity for accurate determination of the incubation period presents itself in the case of laboratory infection Thus in 66 carefully studied and serologically proved cases from Amsterdam the incubation period was 4 to 19 days with an average of 9 6 days (Walch Sorgdrager) The largest number of cases fell into the ten day period (17 cases) There was no difference in the incubation period in the fatal and non fatal the icteric and nonicteric cases

The clinical course of the disease has been divided by most observers into three stages This is useful not only because these stages differ in the salient symptoms and findings but also because they differ in the diagnostic laboratory procedures

First stage (septicemic stage)

As the descriptive term denotes during this stage the spirochete circulates in the blood stream and can be cultured from it It lasts two to nine days—usually five

The onset is sudden and is ushered in by severe headache chilly sensations and marked prostration In a few cases reported from Holland there was not this abrupt onset The headache is usually frontal but may be occipital or bitemporal The chilly sensations may be replaced by a shaking chill (Ashe and co workers) but this is the exception rather than the rule Vomiting is frequently among the first symptoms and diarrhea occasionally Anorexia and dry and coated tongue are some of the other gastrointestinal symptoms muscular aching is marked and is one of the diagnostic complaints This involves especially muscles of the calves and the back and extraocular muscles The abdominal muscles may also be painful and this with the vomiting and high fever may result in an erroneous diagnosis of acute abdomen Respiratory symptoms of cough hiccough and expectoration of blood tinged sputum may result in confusion with pneumonia

Physical examination in the first stage reveals an acutely ill patient with a high temperature (10 to 10 F) The pulse is fast but not as rapid as one would expect from the fever The blood pressure and respirations are normal Conjunctival injection is present in about 60% of the cases The skin is hot and dry Herpes was noted in 15% of the Netherlands cases It is usually hemorrhagic A rash occasionally occurs but as a rule makes its appearance later in the disease The face is often red and puffy The tongue is red around the edges and erosions and ulceration may be noted on the tongue and buccal mucous membrane The tonsils are frequently red and swollen and this along with the cervical adenopathy suggests a streptococcic pharyngitis (Walch Sorgdrager) Adenopathy is considered rare by others (Ashe

et al) The lungs may be normal or reveal moist rales The heart is normal except for tachycardia with a slower rate than is to be expected from the fever and occasionally bradycardia may be present Evidence of capillary damage is infrequent in the first stage, but petechiae and ecchymosis are occasionally observed early in the disease The abdomen shows no abnormalities, but tenderness of abdominal muscles may be confused with intra abdominal pathology and peritoneal irritation The muscle tenderness is most frequent and most severe in the muscles of the legs and back Muscular pain and tenderness is a common but not universal finding in this disease It was recorded in 85% of the large group of cases (319) from Holland and in 63% of cases from the American literature (White and Prevost) Tenderness of the muscles of the neck along with nuchal rigidity leads to a diagnosis of meningitis In the French literature even opisthotonos is described

Meningitis is actually present in Weil s disease and the leptospirosis meningitis due to L icterohaemorrhagiae may be present without the other symptoms and signs of Weil s disease The French refer to this as Spirochetose Meningee pure Cases with predominant meningeal symptoms and without jaundice have also been reported from the Netherlands Cargill and Beeson observed signs of meningitis in 6 of their 14 cases and noted that 41% of reported cases showed these signs They emphasized the diagnostic importance of spinal fluid examinations which will be elaborated upon below The other members of this group of spirochetes frequently cause meningeal involvement This is especially true of L canicola Recently a case of meningitis due to L pomona was reported from Texas (Caffey Dravin and Dine) Twenty four cases of leptospiral meningitis have been reported from Atlanta Georgia (Beeson and Hankey)

Laboratory Findings

First stage

These consist of a leucocyte count of 14,000 to 20 000 Anemia is slight or absent and the platelet count and prothrombin time are normal The urine is scanty and may show only

TABLE 42
Incidence of Individual Spinal Fluid Abnormalities

Abnormality	Number of Examinations	Number Abnormal	Percentage Abnormal
Xanthochromia	29*	27	90
Increased cell count	97	84	87
Increased pressure	43		51
Positive Pandy	44	6	59
Increased protein	52	6	50
Positive Mastic	18	4	2
Low sugar	35	1	3

* Only jaundiced patients are included in this group
W H Cargill Jr and P B Beeson The Value of Spinal Fluid Examination as a Diagnostic Procedure in Weil s Disease Ann Int Med *27* 396 1947

mild albuminuria However even early albuminuria and cylindruria may be marked Blood urea nitrogen may be moderately or markedly elevated (50–150 mg %) Acidosis and abnormal liver function tests usually do not occur in this stage of the disease The cerebrospinal fluid abnormality is at its height between the 5th and 9th day of illness Thirteen of Cargill and Beeson s 14 cases showed abnormal cerebrospinal fluid The commonest abnormality in their cases as well as in those they reviewed (see Table 42) is a pleocytosis of between 6 and 300 cells per cubic millimeter They regard anything above three cells as abnormal The pleocytosis usually does not exceed 100 cells per cubic millimeter with a preponderance of lymphocytes The polymorphonuclear leucocytes may equal the lymphocytes during the first week The other spinal fluid abnormalities are increased pressure increased proteins abnormal colloidal gold curve and occasionally decreased glucose Xanthochromia was found in 27 of 9 patients examined All of these patients were jaundiced and presumably the xanthochromia was due to bilirubin It is claimed that in other forms of jaundice the bilirubin does not enter the subarachnoid space but in Weil s disease this barrier is broken by the inflammation Spirochetes may be cultured from the fluid It can be seen from the above that the spinal fluid abnormalities may be utilized for diagnostic purposes

The finding of the leptospira in the blood by dark field examination culture or animal inoculation is the all important diagnostic pro-

cedure in this stage of the disease These procedures can be utilized only during the septicemic stage (~9 days) Care must be taken not to confuse Brownian movements with the gyrations of spirochetes in the direct examination of blood The injection of 5 cc of blood intraperitoneally into a young guinea pig (175 gm or less) may be used to demonstrate the organism After a period of 10-14 days jaundice develops and the animal dies The leptospirae can be found in the liver kidneys and other organs of these animals

Second Stage (icteric stage toxic stage)

The first stage ends with the disappearance of the spirochete from the blood stream The second stage is ushered in by the appearance of icterus Since some patients never become jaundiced this stage can be said to be absent in them and they go on to the third or convalescent stage There is frequently a drop in temperature preceding the jaundice but the patient becomes more toxic Icterus may appear in the middle of the first week The limits of its appearance are from the second to the ninth day The largest number of patients in the Amsterdam group became icteric on the fifth day In the American literature jaundice is reported in nearly all cases while in the foreign literature it is reported in only about 50% of cases with a variation of 33% to 88 5% This discrepancy between the American and foreign observations suggests either a higher virulence of the American disease or failure to recognize the anicteric form The latter is the more likely explanation The jaundice varies from subicteric tinge to one of marked intensity

The *pathogenesis of jaundice* in this disease is of interest since all three factors responsible for jaundice may be present (1) hemolysis of extravasated blood (tissue hemorrhages) (2) the hepatocellular damage by spirochetes and (3) extrahepatic or intrahepatic bile duct obstruction by the inflammatory process It is probable that any one or all three of the above factors are concerned to a varying degree in the production of jaundice Hemorrhages into the viscera have been described under Pathology The skin in this stage shows numerous ecchymosis and petechiae Ecchymosis also occurs in mucous membranes of the mouth nose and vagina This blood is hemolyzed and the hemoglobin converted into bilirubin The necessary factors are present for a hemolytic (prehepatic) icterus Hyperurobilinuria in the absence of jaundice in some cases further suggests the importance of this mechanism Quantitative determinations of stool and urine urobilinogen would further elucidate this point Sterling reported the presence of 8 0 mg and 719 mg in the urine and stool respectively during one stage of the disease

That *hepatocellular damage* is present in this disease is evident from the pathologic findings as well as liver function tests Thus positive flocculation tests have been repeatedly reported in this disease Sterling showed that in his case in addition to the positive flocculation tests the cholesterol esters were decreased and the alkaline phosphatase was elevated An elevation of the gamma globulin was also demonstrated in this case Chinn and coworkers recently made a comprehensive study of liver function in six cases of Weil s disease They found markedly positive cephalin cholesterol flocculation tests in all but one case the thymol morbidity was less strongly positive an elevation of alkaline phosphatase gamma globulin and prothrombin time depression of cholesterol esters and bromsulphalein retention were noted in some Hepatocellular damage is undoubtedly the major factor in the pathogenesis of jaundice in this disease The hepatic failure may be the crucial factor in the fatal cases

Changes in the bile ducts undoubtedly play a role in jaundice production again demonstrating the difficulty of divorcing completely duct damage from polygonal cell damage Inflammation of the larger bile ducts may produce a mechanical extrahepatic obstruction This however is extremely rare and unimportant The more important site of impairment is edema of or pressure against the finer bile duct radicals within the liver resulting in intrahepatic obstruction Rupture of the finer intrahepatic ducts has also been demonstrated with leakage of bile back into the blood stream

In addition to the jaundice and ecchymosis

the patient appears very toxic, and the temperature again becomes high—103° to 104° When the temperature remains lower the pulse is very rapid and the relative bradycardia of the first stage disappears Cerebral symptoms of lethargy stupor and delirium may supervene A maculopapular or scarlatiniform rash has been described in about 10% of European cases Leibowitz and co workers have recently described a maculopapular rash sparing the face—most marked on the trunk and extremities in two of their cases Pruritus is absent The lungs may show findings similar to those in the first stage The heart tones may become muffled a systolic murmur and pericardial friction rub may also appear The blood pressure remains low in spite of the appearance of azotemia Peripheral circulatory disturbances may be evidenced by cold and cyanotic extremities Muscular tenderness is either diminished or disappears The liver becomes moderately enlarged and tender The spleen however is rarely palpable Iritis and iridocyclitis and optic neuritis are occasionally seen These are usually mild with complete recovery ensuing

The renal changes are most important in this stage for along with the hepatic damage they determine the final outcome Oliguria and anuria may occur The latter is a poor prognostic sign Hematuria may also be present Renal pain and tenderness may be present because of subcapsular hemorrhage

The laboratory findings of greatest importance in this stage are those in reference to (1) renal damage (2) hepatic damage and (3) immunological and bacteriological factors

The urine shows more albumin red blood cells and numerous casts as well as bilirubin and urobilinogen The blood urea nitrogen as well as the creatinine becomes markedly elevated Acidosis is evidenced by a drop in CO combining power

The liver function tests become abnormal as was mentioned before The stools are rarely acholic in spite of intense jaundice

The leptospira appears in the urine This usually takes place at the end of the second week It has been cultured from the urine on the ninth day Thus after the septicemic first stage the specific organism is to be looked for in the urine Leptospiruria may persist for weeks or even months During this period the specific antibodies begin to rise in the blood stream A positive agglutination titer should be 1 300 or above Diagnostic titers are usually not obtained until the 14th day rapidly increase to the 21st day and may remain elevated for years

In addition to the above important laboratory findings the leucocyte count may be increased in this stage to as high as 50 000 Anemia of moderate degree develops because of the hemorrhagic tendency The prothrombin time may remain normal as well as the platelet count and clot retraction although abnormalities in all three have been described Chinn and co workers have reported a prothrombin of 17% in one patient and 22% in another one

Third stage (convalescent stage)

If death does not occur convalescence begins between the 14th and 16th day and may proceed rapidly The fever and signs of toxicity subside Diuresis with a fall in urea nitrogen and decrease of icterus mark this phase The icterus may be the last symptom to disappear Convalescence may be prolonged for several weeks Alopecia has been observed in males during this period

Relapses are characteristic of this disease and occur in 28% to 75% of cases In the 3rd or 4th week when the patient has become afebrile and nearly asymptomatic a rise i temperature with mild systemic symptoms may occur This lasts for several days These relapses are not serious Jaundice and azotemia do not return As many as three or four relapses may be experienced and are as frequent in the anicteric as in the icteric disease While the leptospira has never been recovered from the blood during a relapse it has been recovered from the spinal fluid Thus it may actually be a bacteriological relapse

Clinical Features—Summary

Incubation period 4 to 19 days (over 10)
Stage 1 (septicemic stage 2 to 9 days)
Onset abrupt
Symptoms
Headache

Chilly sensations
(chills occasionally)
Vomiting
Muscular aches
Cough
Bloody expectoration
Physical Findings
High fever 102–106
Conjunctivitis
Herpes (15% of cases)
Petechial hemorrhages (usually later)
Muscle tenderness
Meningeal signs

Laboratory Findings

Urine scanty—mild albuminuria
Blood urea nitrogen—50 to 150 mg %
CNS fluid
pleocytosis
increased pressure
Pandy plus
Xanthochromia (due to bile—later)
Leptospiremia by
direct smear
culture
guinea pig (young—175 gm) inoculation
Stage 2 (icteric toxic stage)
Symptoms and findings
Icterus appears
Liver enlarged and tender
Renal oliguria anuria
Cerebral symptoms (lethargy stupor delirium)
Rash maculopapular (10% of cases)
Hemorrhages petechial ecchymotic—skin and mucous membranes
Gastrointestinal tract epistaxis
Heart tones distant
Peripheral circulatory disturbances
Ocular changes (iritis iridocyclitis optic neuritis)
Laboratory findings
Renal damage—urine scanty albuminuria cylindruria bilirubinuria urobilinuria
blood—urea nitrogen and creatinine rises acidosis CO combining power
Liver function tests abnormal
Bacteriological leptospiruria (may persist for weeks or longer)
agglutination titer rising—1:300 significant usually not before the 14th day
Stage 3 (convalescent)
Begins 14th to 16th day
Rapid improvement
fever
toxicity
jaundice (last to disappear)
diuresis
alopecia in males occasionally
Relapses 28 to 75% of cases
begin in third or fourth week
one to four not serious
no jaundice or azotemia
no leptospiremia
spinal fluid may contain spirochetes

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The disease is undoubtedly commoner than a perusal of the American literature would indicate. Its diagnosis is based upon (1) history of exposure to rodents or their excreta (2) sudden onset of a febrile illness with prostration headache muscular pain tenderness and conjunctivitis followed by (3) icterus petechial and ecchymotic hemorrhages (4) azotemia with normal blood pressure (5) meningeal signs with abnormal and icteric spinal fluid (6) leptospiremia in the first week (7) leptospiruria after the ninth day (8) high and rising agglutination titer after the tenth day of illness (9) muscle biopsy showing characteristic changes.

It has to be differentiated from other hepatic diseases (hepatitis cirrhosis) other systemic infections diffuse renal diseases and meningitis. The marked azotemia which begins before the hepatic changes differentiates it from hepatitis and the cirrhosis. In the latter disease renal involvement (hepatorenal syndrome) may occur but is a late manifestation of cholemia. The meningeal signs and spinal fluid changes are further differential features. Cases of systemic infection such as typhoid or para-

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typhoid fever show a preponderance of gastro intestinal signs and symptoms Renal involvement consists only of mild albuminuria The bradycardia and leukopenia of typhoid are distinctive The meningeal signs and findings are not found in these systemic infections The differentiation from yellow fever may be difficult but is not important in this country Relapsing fever may pose a difficult diagnostic problem The finding of spirochetes in the blood would require their specific identification But the exposure to a tick or louse the localized distribution in this country the relative infrequency of jaundice and the characteristic crisis and relapses should aid in clinical differentiation

Malaria especially when accompanied by jaundice may confuse the diagnosis however the characteristic fever shaking chills and leukopenia will lead to finding the Plasmodium in the blood Typhus fever is not important in this country but other rickettsial diseases may have to be considered

Glomerulonephritis does not show the marked prostration or the sudden onset the urinary findings are more classical and hyper tension accompanies the azotemia The spinal fluid findings would differentiate it promptly from other types of meningitis The bacteriologic and immunologic determinations clinch the diagnosis

Differential Diagnosis—Summary

1 **Other hepatic diseases**
   - **hepatitis**
   - **cirrhosis**
   - **hepatic syphilis**
   - **tuberculosis**
   - **liver abscess**

2 **Systemic infections**
   - ***influenza (in anicteric stage)***
   - **typhoid fever**
   - **paratyphoid fever**
   - **yellow fever**
   - **relapsing fever**
   - **malaria**
   - **typhus fever**

3 **Renal disease**
   - **glomerulonephritis**
   - **pyelonephritis**

4 **Meningitis**
   - **meningococcic**
   - **tuberculous**
   - **purulent**
   - **influenzal**

Complications

Other diseases may complicate Weil s disease by virtue of contaminated water supply or poor sanitation Thus typhoid and paratyphoid fever have complicated this disease Malaria has also been mentioned Purulent meningitis and tuberculous meningitis have been reported The skin may become infected with staphylococci and furunculosis results Leptospiral endocarditis is a most serious complication True myocarditis may develop Nervous system complications such as neuritis and myelitis have been observed

Prognosis and Cause of Death

The mortality rate in this country has been about 30% The mortality rate depends upon the following factors (1) age of patient (Table 43) (2) presence of icterus (3) degree of azotemia (4) cardiac function and (5) extent of hemorrhagic phenomenon The unfavorable influence of age on prognosis is graphically illustrated by the table of Walch Sorgdrager The mortality of patients under 40 was 7% but in those over 60 it was 60% Death is rare in anicteric Weil s disease "When there is no jaundice there is no death" Anuria and rapidly advancing azotemia as well as rapidly failing hepatic function are of *serious prognostic* significance Signs of serious cardiac weakness manifested by either marked tachycardia or

Table 43

The Relationship of Age to the Mortality Rate in Weil s Disease

Age Group	Number of Patients	Died	Fatality Rate
1 to 10	11	0	0%
10 to 40	210	15	7 1%
40 to 60	49	1	4%
60 and over	15	9	60%
Unknown age	85	8	
	370	44	11 9%

B Walch Sorgdrager Leptospiroses Bull Health Organization of League of Nations 8 143 1939

bradycardia, falling blood pressure and vascular collapse are poor omens Severe bleeding from the gastrointestinal tract is serious

When death occurs it takes place between the 9th and 16th day This is most commonly due to hepatic or renal failure or both Cardiac death may be due to myocarditis hemorrhage into the myocardium or spirochetal endocarditis Death may also be due to severe hemorrhage

Treatment

As in the treatment of all infections supportive therapy including absolute bed rest good nursing care and adequate fluid and caloric intake must be insisted upon The oliguria may be accentuated by dehydration from the high fever and vomiting Parenteral fluids containing glucose not only may supply fluid and calories but may help to minimize the hepatic injury Proteins should be given orally or parenterally as amino acids Ascorbic acid and the B complex should supplement the diet I fail to see the rationale of using vitamin K for the hemorrhagic phenomenon in the presence of a normal serum prothrombin value If the anemia from the hemorrhage becomes severe replacement by blood transfusion becomes necessary

Specific Therapy

The administration of immune serum and antibiotics is the specific therapy Experience with immune serum is scant in this country because of the lack of availability The serum is derived from horses whose agglutination titer against the leptospira has been raised to 1 100 000 It is given in a dosage of 60 cc according to the experiences in the foreign literature it lowers the mortality rate appreciably if given within the first six days of illness Blood transfusions from immune donors have been used in this country with apparent benefit Blood transfusions from immune donors are recommended highly by Patterson who thinks they should be more effective than horse serum by virtue of the erythrocyte content While the absence of serum reactions with human blood is an additional virtue the possible transmission of serum hepatitis by this means to a patient with established hepatic injury may raise a serious problem

Antibiotics

Penicillin because of its effectiveness in other spirochetal diseases (syphilis and relapsing fever) would be expected to be effective in Weil s disease It has been used in experimental leptospirosis in animals with good results Some have claimed merely a suppressive effect in guinea pigs when given before severe clinical manifestations The effect is not considered curative by these workers (Augustine et al) Chang concluded that penicillin has a leptospirostatic but no leptospirocidal effect both in vivo and in vitro and agrees that it is most effective before the appearance of jaundice Larson and Griffith found immune serum and penicillin equally effective in experimental leptospirosi but found both agents ineffectual by the time jaundice appears These laboratory observations emphasize the need for early diagnosis of this disease in the first stage (before jaundice) if therapy is to be effective An early diagnosis is a most important therapeutic agent

In human Weil s disease penicillin appears to be effective and should be administered early Patterson used it in six patients 15 000 u every three hours intramuscularly Bulmer reported its use in British troops in Normandy in higher dosage (40 000 u every three hours) Among 16 patients treated (during the icteric stage) with the antibiotic there was one death while among 23 treated without penicillin two deaths occurred This is not conclusive However there was a more rapid drop of temperature and fewer febrile relapses in the treated groups To prevent relapses the antibiotic should not be stopped too quickly

Aureomycin has been found more effective than penicillin in experimental leptospirosis and its use in clinical cases should be encouraged Aureomycin and penicillin were recently used successfully in a case of canicola fever (Whitehouse 1951) Sulfonamides seem to be ineffective in this disease A gloomy therapeutic note is struck by a recent report by Hall and co workers (1951) 67 patients with Weil s disease were treated with chlor

amphenicol, aureomycin penicillin terramycin streptomycin and cortisone plus aureomycin They conclude that none of these drugs are effective in Weil's disease although they reiterate the difficulty in evaluating a therapeutic agent in a disease that shows such great variation in severity

An interesting therapeutic approach was utilized with success by Williams He used Nupercaine intrathecally to produce spinal anesthesia in a 61 year old man with severe oliguria and deep icterus The patient recovered dramatically The rationale of this procedure consisted of interruption of the vasomotor nerves to the renal arterioles which may be in a state of spasm

31—*Tuberculosis of the Liver*

THE invasion of the liver by the tubercle bacillus may present certain manifestations that focus the attention of the clinician on this organ to the exclusion of the primary focus Tuberculosis of the liver is rarely primary This can occur only by *prenatal infection* of the liver through the placental circulation Secondary tuberculosis of the liver is an extension from a primary focus in the lungs or more rarely primary gastrointestinal tuberculosis

The tubercle bacillus may reach the liver by the following pathways

I Hematogenous
  A Hepatic artery—brings the bacillus from the lungs
  B Portal vein
    1 drainage of intestinal focus
    2 rupture of lymph node directly into vein
II Lymphogenous
  A Intra abdominal focus draining into the liver
  B Lymphatic retrograde extension through diaphragm (?)
III Bile ducts
  A Rupture of tuberculous lymph node into bile ducts and thence into the liver
  B Ascending tuberculous cholangitis (rare)
IV Direct extension
  Through Glisson s capsule from intra abdominal focus

It has been suggested that tubercle bacilli reaching the liver via the hepatic artery give rise to acute miliary tuberculosis while those entering the liver via the portal vein give rise to the more chronic localized form This prompts the question whether the liver cells develop a resistance against the organism from the abdominal cavity or whether these organisms become attenuated in the abdominal organs Some have doubted lymphatic spread of the tubercle bacillus through Glisson s capsule into the liver since the lymphatic drainage is into the porta hepatica and away from this organ

Pathology and Pathogenesis

There are three anatomical forms of hepatic tuberculosis that have clinical significance as well (1) miliary tuberculosis ( ) massive tuberculomata (cold abscess) and (3) tubular tuberculosis or tuberculosis of the bile ducts Miliary tuberculosis of the liver as part and parcel of hematogenous spread from the lung is the commonest anatomical form Involvement of this organ is second only to the spleen in its frequency *(Chapman and Wharton)*

According to Boyd tuberculous involvement of the liver may be found in every case of miliary tuberculosis Calcified areas in the liver and spleen may indicate a healed tuberculous infection in these organs Correlation of the frequency of liver involvement in other localizations of the tuberculous focus by Lewison Froelich and Ragins brings out some curious aspects of the problem They found that in 21% of their cases of pulmonary tuberculosis the liver was involved but this increased to 37% in miliary tuberculosis and 59% in tuberculous meningitis The last figure 59% is probably the more probable figure for miliary tuberculosis and obviously hematogenous dissemination must have occurred for the meninges to be involved Likewise in pulmonary tuberculosis if liver involvement is present a hematogenous spread must have taken place at some time unless the tubercle bacilli reached the liver via the gastrointestinal tract However this appears from their figures to be a rare avenue for only one of their six patients with tuberculous enteritis (16 6%) showed hepatic involvement Crawford and Sawyer however found the liver only second to the spleen in the frequency of intra abdominal organs involved in intestinal tuberculosis In 645 cases of intestinal tuberculosis the liver was involved 169 times or 25%

Anatomic changes include enlargement of the organ but the tubercles may not always be visible to the naked eye (Fig 38) Some of them may be rudimentary and consist of merely endothelial cells Of course typical caseating tubercles and giant cells have to be found for establishing a diagnosis The tubercles are most frequently found in the portal triads in relationship to the bile ducts (Boyd)

Massive tuberculomata are very rare lesions and consist of solitary or multiple large caseating areas These may resemble grossly necrotic neoplasms or

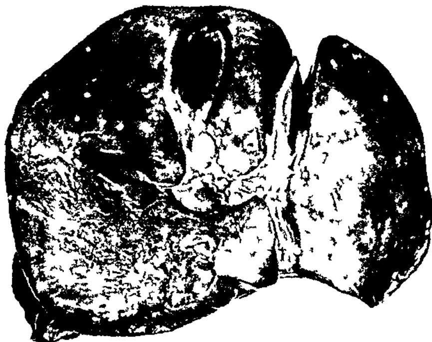


Fig 38 M y b u o of he l e Th wh as re be l s n al l b s of he l er
Th pa n w s a N gr mal age 35 who compla ed of a co gh f vee ja ndice two e s b fo e d m s on w gh l 2 lbs bdom l enla g ment 8 mo h Ph al x m on re ea ed em ciated ch n ca ly j nd d p e t p pable c rv l odes abdom al d ten n p lpable l e and spleen Serum b l rub 5 mgm% Th m l b d y 9 n ts To l p o e ns 7 9 gms A bum n 3 2 gms Glob l n 4 7 gms A k ne ph ph a e 135 Boda ky n s To l ch le rol 256 mg% Es rs 36 mg% Sputa n ga e o h b le b c l s (Th s figur nd figures o 11 2 4 6 4 43 57 nd 80 a f om exh b t by Sp b g B nn M m n and B k r A M A Con n on June 95 A la C y N w Je s y)

gummas and reach the size of an orange The tuberculomata may be so numerous as to destroy all the liver tissue and give the organ a honeycomb appearance On section the necrotic tissue may pour out leaving an empty cavity Thus a cyst or an abscess is simulated Indeed the term cold abscess has been applied to them The wall of these cavities may consist of a thick fibrous capsule Microscopically typical tubercles are found in the capsule The pathological diagnosis may be difficult and tubercle bacilli should be demonstrated to differentiate these lesions from gummas Fatty changes in the liver cells are frequently noted and changes compatible with portal cirrhosis have been reported The cirrhosis however is not directly attributable to the tuberculous infection

Other organs are almost always involved in the tuberculous process The lungs may show miliary tuberculosis and the gastrointestinal tract may be involved Caseating tuberculous lymph nodes are frequently found in the porta hepatica and other areas in the abdomen Ascites may be present in the absence of tuberculous peritonitis This was the case in Ashton s patient Apparently in two of the cases reported in the literature the primary tuberculous foci had healed and escaped detection hence the term primary was used to apply to the hepatic process One of these was associated with a hydatid cyst (cited by Ashton)

Tubular tuberculosis of the liver is very rare Three cases of this entity were described by Rosenkranz and Howard who also reviewed the literature The gross lesions are confined to the intrahepatic bile ducts although miliary tubercles are found in the hepatic parenchyma on histologic examination There has been much discussion about the pathogenesis of this lesion The consensus is that it even more than in the other forms of hepatic tuberculosis occurs in individuals with low immunity and may represent an early hematogenous spread It is also contended that the tubercle bacillus does not arrive directly from the lung through the hepatic artery rather an intra abdominal or intestinal focus is formed The intestinal focus may be primary Even if an intestinal focus is not found the possibility of a healed tuberculous ulcer cannot be excluded The bile ducts may be invaded by lymphatic drainage by rupture of a caseating lymph node into a bile duct or through the portal vein Ascending cholangitis has also been invoked as a possibility but this is extremely unlikely since tuberculous lesions of the larger extrahepatic bile ducts are not found The possibility has also been put forth that intrahepatic cholangitis is produced by the spread of tubercle bacilli from the sinusoids into the bile capillaries However as has been pointed out before in miliary tuberculosis of the liver the tubercles are frequently situated in the portal triads near the bile ducts and the latter may be involved secondarily

Grossly these livers appear to be smaller than normal Solitary or multiple caseating areas are found mixed and stained with bile and are proved microscopically to be tubercles within bile ducts Other caseating tubercles are found adjacent to and ulcerating into bile ducts Microscopic tubercles unrelated to bile ducts are also found

Pathology—Summary

- I Miliary Tuberculosis—commonest form
  - A Hematogenous spread from lungs
  - B Liver enlarged
  - C Tubercles may be microscopic in size—found in portal triads in relationship to bile ducts
- II Massive Tuberculomata—very rare
  - A Solitary or multiple large caseating areas
  - B Grossly resemble neoplasm or gumma
  - C Liver has honeycomb appearance when lesions are numerous
  - D *Cirrhosis* may be associated with it
  - E Ascites may develop
- III *Tubular Tuberculosis*
  - A Gross lesions confined to intrahepatic bile ducts
  - B Small tubercles may be found in adjacent hepatic parenchyma
  - C Arises from intra abdominal focus
  - D Bile ducts invaded by
    - 1 lymphatic drainage
    - 2 rupture of caseating lymph node
    - 3 ascending cholangitis

Clinical Features

Miliary Tuberculosis of Liver

Hepatic tuberculosis would be of no clinical importance if it always presented itself in the setting of outspoken miliary tuberculosis In miliary tuberculosis the liver is involved in 50 to 80% of cases hence this form is of frequent occurrence Even in miliary tuberculosis the hepatic involvement may be most conspicuous while the pulmonary disease and especially other organ involvement remains clinically obscure Thus in the cases reported in the literature as well as in the cases ob

served by the author the clinical features were those of sepsis and hepatomegaly

Symptoms

The patient is most likely to be a young person and a Negro The presenting complaints are chills a chilly sensation and fever These symptoms usually persist for a long period of time The temperature may be nearly normal in the morning when the patient feels relatively well Anorexia may be severe and there is nearly always loss of weight This may be reported even in the absence of anorexia Upper abdominal or right upper quadrant pain along with postprandial distention and anorexia may be present Diarrhea may be associated with intestinal tuberculous involvement but constipation or normal bowel activity is just as likely The respiratory symptoms may be very mild or completely absent There may be no cough at all or only slight cough completely overlooked by the patient Cough may be present at the beginning of illness and then completely disappear

Physical Findings

Jaundice may be present and may be marked It results from extensive parenchymal involvement from compression of intrahepatic bile ducts or from compression of extrahepatic bile ducts by enlarged lymph nodes at the porta hepatica Thus the jaundice may be of the hepatic or posthepatic type

The temperature may rise to 103 to 104 in the evening and be normal or nearly normal in the morning There may be drenching sweats reminiscent of malaria

The liver is usually enlarged may reach to the umbilicus and is slightly tender There is no gross nodularity in this form of tuberculosis

The spleen may be slightly enlarged

Ascites may be present and the ascitic fluid may be clear yellow or greenish This may be a true transudate and may be present in the absence of tuberculous peritonitis

The lungs may show no abnormality on physical examination or reveal a few rales Cervical and axillary lymphadenopathy may be detected Some of these nodes may be very hard and calcified

Massive Tuberculomas and Tubular Tuberculosis

These forms of tuberculosis are rarer than the miliary type but in spite of this are of greater interest because they are more likely to suggest primary hepatic disease The extrapulmonary involvement is even more obscure Morris in 1930 found a total of 11 cases in the world literature and only three in the American literature Since then a few more cases were reported Pagel (1938) Herrell and Simpson and Ashton reported one case each

The clinical picture in these two varieties is very similar to that found in miliary tuberculosis with a few variations In massive tuberculomas the liver in addition to being enlarged may reveal nodularities or gross irregularities suggestive of a neoplasm These areas may be tender In the tubular variety the liver may be small but jaundice may be more marked

Clinical Features—Summary

- I Miliary Tuberculosis
  - A The liver changes may dominate the clinical picture
  - B Commonest in young Negroes
  - C Symptoms
    - 1 Chills or chilly sensations
    - 2 Anorexia
    - 3 Weight loss
    - 4 Pain in upper abdomen or right upper quadrant
    - 5 Bowel movements vary from diarrhea to constipation
  - D Physical Findings
    - 1 Jaundice of hepatic or post hepatic type
    - 2 Fever—evening rise
    - 3 Liver enlarged and slightly tender
    - 4 Spleen may be slightly enlarged
    - 5 Lungs may be negative
- II Massive Tuberculomas—Tubular Tuberculosis
  - A Similar to above with following exceptions
    - 1 Massive tuberculosis—grossly nodular liver simulating neoplasm

2 **Tubular variety—liver may be small, but jaundice is more marked**

Laboratory Findings

The blood may show slight anemia The leukocyte count is usually normal or shows only a slight elevation which in the face of the high septic fever is of considerable diagnostic importance

Liver function tests are only slightly deviated from the normal An almost constant finding is a slight elevation of the total proteins to 8 0 gm % with increase of the globulin fraction although low total proteins were reported by Wolf and Flory The alkaline phosphatase is frequently slightly elevated this does not depend upon skeletal involvement

Bromsulphalein retention has been noted The flocculation tests are either normal or only slightly positive Prothrombin of 11% of normal was noted in the markedly debilitated patient by Wolf and Flory

The tubercle bacillus should be looked for in the sputum gastric contents and stools If direct smears do not yield positive results cultures should be obtained Positive blood culture has been reported (Wolf and Flory) It should be emphasized that the tubercle bacillus may be difficult to find

X ray findings indicative of pulmonary tuberculosis are frequently found Occasionally calcifications in the region of the spleen and liver may be found

Liver biopsy may be the one diagnostic finding (Fig 39) and in recent years needle biopsy has been found to be a useful procedure in this disease In the older literature the diagnosis was usually established at laparotomy or autopsy

Biopsy of a peripheral lymph node may help to establish the diagnosis of tuberculosis but does not positively identify the hepatic lesion



Fig 39 Tuberculosis of liver Needle biopsy (× 100) demonstrating a tubercle with Langhan giant cells and epithelioid cells within the hepatic parenchyma A tubercle bacillus was demonstrated by special stains The diagnosis was made by the liver biopsy (p 6 case 4)

Laboratory Findings—Summary

Blood—anemia—normal leukocyte count
Liver Function Tests
Total Protein—elevated increase only in globulin fraction
Alkaline Phosphatase—elevated
Bromsulfalein retention
Flocculation Test—mildly positive
Prothrombin Time—occasionally elevated
Tubercle Bacillus
Should be looked for in sputum gastric washings and stools
Liver Needle Biopsy
Most important diagnostic tool
Biopsy of lymph node may aid in diagnosis

Diagnosis

The following case reveals the difficulty of making a diagnosis of hepatic tuberculosis and the importance of liver biopsy

Case 4

A Negro age 5- complained of fever of six weeks duration loss of weight of 30 lb and weakness This began with chilly sensations followed by a temperature of 101 to 10- This recurred daily with the temperature rising in the afternoon and returning to normal in the morning Defervescence was accompanied by marked diaphoresis Loss of weight was

claimed to have taken place in spite of a good appetite. Constipation had been present for 8 to 10 years. Cough, chest pain and hemoptysis were absent.

Physical examination revealed a chronically ill individual. Palpably enlarged cervical, axillary and inguinal lymph nodes were present. The lungs were normal except for a few crepitant rales in both axillary regions. The liver was enlarged to a point four fingerbreadths below the costal margin and extended over to the left hypochondrium. It was hard, not nodular and slightly tender. The spleen was barely palpable. Rectal examination revealed a firm irregular extraluminal mass anterior to the rectum and above the prostate. Sigmoidoscopic examination confirmed the extraluminal character of this mass and the absence of mucosal involvement.

Skin tests with purified protein derivative, second strength, was strongly positive. The Frei test was negative and the Kahn test positive.

Laboratory examinations revealed mild anemia, 3.64 million erythrocytes, hemoglobin of 68% and 6,950 leukocytes with 66% polymorphonuclear cells. Serum glucose, urea nitrogen, chlorides, CO_2 combining power, sodium and potassium were normal.

Liver function tests revealed a serum bilirubin 0.5 mg %, total protein 8.8 gm (albumin 6 gm and globulin 6 gm %), cholesterol 1.6 mg with 59.6% esters, thymol turbidity 1.5 units and thymol flocculation 0. Cephalin cholesterol flocculation was 2 plus. The bromsulphalein test showed no dye retention after 45 minutes.

X-ray examination of the chest showed a 1 to 2 cm nodular density in the left first interspace anteriorly. Bronchovascular markings were exaggerated and hilar calcification was present. Gastrointestinal x-ray series was negative, as was an intravenous pyelogram.

Smears of sputum, material from bronchial lavage and stools were negative for acid-fast bacilli. Culture of sputum revealed tubercle bacilli.

Liver biopsy with the Vim Silverman needle revealed typical tubercles with giant cells, epithelioid cells; an acid-fast bacillus was identified in one of them (Fig. 39). The pathological diagnosis was tuberculosis of the liver.

This case is representative of the diagnostic problems encountered in hepatic tuberculosis. Systemic diseases such as malaria have to be considered. Lymphoma or carcinoma with metastasis comes into consideration because of hepatic and lymph node enlargement and the rectal mass. The minimal findings in the lungs, the absence of respiratory symptoms and the absence of tubercle bacilli in sputum on direct smear made the diagnosis of tuberculosis doubtful. The crucial importance of liver biopsy was demonstrated in this case. The demonstration of the tubercle bacillus in the liver sections differentiated the disease from syphilis, which had to be considered because of the positive Kahn test.

Other diseases with which this condition has been confused are pyogenic liver abscess, amebic abscess, cholecystitis and empyema of the gallbladder. The normal leukocyte count should help to rule out these conditions. Other systemic infections such as typhoid fever, tularemia and subacute bacterial endocarditis may have to be considered. Bacteriological and immunological tests will serve to differentiate these conditions. In the presence of severe jaundice, even Weil's disease or infectious hepatitis may pose a problem. This possible confusion was pointed out by Warthin in 1908.

Treatment and Prognosis

The modern therapeutic agents (streptomycin, dehydrostreptomycin and the sodium salt of para-aminosalicylic acid) may produce better results than has been possible in the past. The former may be used in 1 gm doses intramuscularly daily and the latter in divided doses, 12 gm a day. Our patient showed clinical improvement shortly after institution of this therapy. Isoniazid (isonicotinyl hydrazide) in a daily dose of 3 to 5 mg per kilogram should be used in combination with the above.

The prognosis in these cases has been probably unduly pessimistic in the past. The finding of calcification in the spleen and liver in apparently healthy individuals is a sign that hepatic miliary tuberculosis has healed. The pessimism

in the literature is dependent upon impressions obtained from terminal cases The newer therapeutic agents should make the prognosis more favorable

Herrell and Simpson s case (1939) is most unusual from the point of view of prognosis and treatment Their patient had intermittent episodes of chills and fever for six years Surgical exploration revealed a mass in the liver grossly suggesting a neoplasm Biopsy of that area yielded a thick exudate of pus and necrotic material The *histologic examination of the* tissue showed tuberculosis The patient improved after the laparotomy

32 *Brucellosis*

THIS specific systemic infection with Brucella abortus or Br suis which is also known as undulant fever Malta fever Mediterranean fever Bang s disease produces a lesion in the liver with greater frequency than is ordinarily realized These changes while not the most important feature of the disease are nevertheless of great importance to the pathologist as well as the clinician

Pathology

Only the changes in the liver will be discussed in detail here Since it is a systemic bacterial infection it is to be expected that many of the organs would be involved Harris in his monograph on brucellosis lists -5 organs that show pathologic changes He refers to the liver as being enlarged in most cases and showing cloudy swelling areas of necrosis and degeneration especially around the central veins He mentions round-cell infiltration in the interlobular fis ures but refers to epithelioid cells as being seldom found and not compressed into aggregates Infectious granulomas are mentioned by *him but he does not refer to their presence in the* liver

*The formation of granulomatous lesions in experi*mental brucellosis in guinea pigs was observed three and four decades ago by Fabyan and Jaffe Granulomatous lesions in the human liver were emphasized in the foreign literature but neglected in *the American literature Mettier and Kerr however* found such lesions on biopsy of the liver in one of their patients They referred to the microscopic changes in this organ as a bizarre inflammatory destructive process with cellular reaction around a granulomatous process A larger granuloma showed at the center cellular debris and disintegrating leucocytes surrounded by vascular connective tissue epithelioid cells lymphocytes and multinucleated giant cells Numerous small tubercle like *lesions composed of lymphocytes epithelioid and giant cells were seen in parenchymal spaces* These were surrounded by fibrous tissue Lowbeer also described a case showing granulomatous lesions in the liver and gallbladder The clinical features of these cases will be discussed below

Spink and co workers discussed in detail liver biopsies of ten patients with brucellosis and the pathology of one autopsy This significant contribution focuses our attention on the hepatic changes in this disease Four of these biopsies were obtained surgically four by needle and two peritoneoscopically In all the specimens *granulomas* were found in the portal areas or within the lobules These granulomas varied in size and consisted of lymphocytes epithelioid cells and giant cells Occasionally giant cells were absent These leso s are indistinguishable from other granulomas such as Boeck s *sarcoid tuberculosis or syphilis Other lesions* observed were lymphocytic infiltration of th portal spaces mild fatty changes occasional necrotic parenchymal cells and golden brown iron-containing pigment in some liver cells

A remarkable fact about these observations *is the* uniformity with which the granulomatous lesion was found regardless of the clinical state of the patient Spink and co workers properly conclude that this *lesion represents a response of the host to the organ*ism and not a complication They regard the epithelioid granuloma as a response to an organism of low virulence such as Br abortus which wa *found*

in all their cases Br suis and Br melitensis which are more virulent may not be expected to evoke this response Lowbeer however cultured Br suis from his patient who showed granuloma in the liver and gallbladder Thus the response with granuloma formation may depend not only on the low virulence of the organism but on the degree of resistance of the tissues of the host

The possible relationship of this infection to cirrhosis of the liver is the most intriguing part of the entire problem In the material presented by Spink and co-workers only one specimen showed slight fibrosis Of Cohen s 53 patients one died with a cirrhotic liver Microscopically this liver showed extensive periportal fibrosis fatty degeneration and hyperplasia of bile ducts Rothenberg s patient died with ascites and atrophic cirrhosis While the exact role of brucellosis in the genesis of cirrhosis in these cases cannot be determined it is very likely that an infection which involves the liver with such frequency and so characteristically could play at least an accessory role in the causation of cirrhosis

McCullough and Eisele recently reported a remarkable case of prolonged severe Brucella hepatitis showing extensive focal necrosis with minimal granuloma formation progressing to cirrhosis Tissue was obtained for microscopic study during the acute stage which lasted about eight months and in the chronic stage two years after convalescence There was no other obvious causative factor in the development of cirrhosis in this patient It seems reasonable to postulate that Brucella infection may be a major factor in the development of cirrhosis in some and a contributory factor in others

Pathology of Brucella Hepatitis—Summary

Granulomas (Periportal and Intralobular)
- **Consisting of**
  - **Lymphocytes**
  - **Epithelioid cells**
  - **Giant cells**
  - **Not distinguishable from other granulomas (Fig 40)**

Lymphocytic portal infiltration
Fatty changes
Focal necrosis
May lead to cirrhosis

Clinical Picture

Involvement of the liver may be present in the absence of any symptoms referable to this organ However abdominal distention anorexia and nausea as well as upper abdominal pain may be due to the hepatic localization of the disease That liver enlargement and tenderness are frequently present during active phases of the disease can be surmised from the pathology Indeed we have seen hepatic enlargement as the principal finding which may eventually lead to the diagnosis Of Cohen s 53 patients 38 had palpable livers 2 of which were definitely enlarged Right upper abdominal pain may be severe and simulate cholecystitis Surgery may be erroneously performed for this as happened in Lowbeer s case Mettier s patient showed the clinical picture of cholecystitis Inflammation of the gallbladder and common duct can be expected from the fact that the organism can be cultured from the bile of these patients

Jaundice is uncommon but may occur primarily because of the hepatocellular damage but edema of bile ducts may be a contributory factor

Ascites may occur and along with the hepatic enlargement leads logically to a diagnosis of cirrhosis While cirrhosis may indeed be present the case reported by Zaus and Espey suggests that the process may be entirely reversible and be due entirely to the acute infection The liver of their patient was visualized peritoneoscopically and did not appear to be nodular The ascitic fluid was clear and had a specific gravity of 1 010 signifying a transudate The patient reported by McCullough and Eisele developed cirrhosis which was clinically quiescent

Splenic enlargement is probably commoner than hepatic enlargement

Laboratory Findings

Liver function tests may show some degree of abnormality in about half of the cases Five of Spink s cases showed normal liver function the other six showed one or several *abnormalities in the following tests* elevation of serum bilirubin increased urine urobilinogen coproporphyrin positive thymol turbidity cephalin cholesterol flocculation and increased bromsulphalein retention An elevation of the serum globulin especially the gamma fraction may be seen

Anemia of severe degree may be present this may be due to hemorrhages into various tissues or to a hemolytic process This may contribute

to urobiligenuria and to hyperbilirubinemia Leukopenia is the rule but occasionally mild leukocytosis may be seen

Diagnosis

The hepatic involvement in this disease may result in confusion with cirrhosis hepatitis, cholecystitis and other primarily hepatic con ditions However involvement of this organ may yield an additional means for the diag nosis of brucellosis Thus in two of our cases a needle liver biopsy revealed a granulomatous lesion compatible with this disease which was proved by further bacteriological studies (Fig 40) Culture of the tissue removed from the liver may be positive while blood cultures are sterile The findings of tubercles or granuloma requires differentiation from sarcoidosis tuber culosis and syphilis If the patient is exposed to cattle gives a history of drinking raw milk and has persistent fever and leukopenia specific bacteriological and immunological studies have to be carried out These consist of blood sternal marrow and liver culture guinea pig inocula tion agglutination tests opsonocytophagic in dex and intradermal test Ascitic fluid and bile may give positive cultures of the organisms Final bacteriological proof may be difficult to obtain because of cultural pitfalls and an occasional case will not show an elevated agglutination titer



Fig 40 Brucellosis Needle biopsy of liver (X 100) demonstrating granulomatous lesion with multinucleated giant cells. The liver was palpable but not markedly enlarged The liver biopsy led to the final diagnosis

Therapy

The avoidance of raw milk from infected cattle and elimination of sick animals would adequately prevent the disease

Active treatment for the acute episodes consists of administration of one of the newer antibiotics chloramphenicol (Chloromycetin) 4 0 gm the first day followed by 2 0 gm daily thereafter aureomycin and terramycin 2 0 gm daily Individual doses continued for two weeks are effective The fever usually stops after two to three days of therapy but relapses may occur in about 30% of cases These can be controlled by the above therapy

To protect the liver from permanent dam age it is important not only to reduce the relapses to a minimal period of time but also to insist on proper nutrition

Brucella Hepatitis—Summary

Clinical Features
- **Abdominal distention**
- **Anorexia vomiting**
- **Abdominal pain upper abdominal and right upper quadrant may simulate cholecystitis or acute abdomen**
- **Liver enlarged and tender**
- **Spleen enlarged**
- **Jaundice uncommon—but occurs**

Laboratory Features
- **Liver function test**
  - **Hyperbilirubinemia**
  - **Urobiligenuria**
  - **Coproporphyrinuria**
  - **Thymol turbidity** } positive
  - **Cephalin cholesterol flocculation** } positive
  - ***Bromsulphalein retention***
  - **Globulin elevation**
  - **Albumin depression**
- **Anemia—may be slight or marked**
- **Leukopenia**

Diagnostic Test
- **Positive and rising agglutination titre**
- **Culture of blood marrow or liver tissue**
- **Liver biopsy**

Malaria

MALARIA occupies a unique position among infectious diseases as far as its effect on the liver is concerned The following factors may be instrumental in producing liver injury

1 Direct effect of the parasite
2 The concomitant anemia
3 The excessive pigment production (from hemolysis) results in (a) increased excretion and (b) increased storage
4 Prolonged fever
5 Antimalarial drugs

The use of induced malaria for therapeutic purposes has offered a unique opportunity for studying some aspects of this problem

Pathology

The liver is almost uniformly enlarged to a moderate degree Its color after prolonged infection is slate gray or blackish This discoloration is seen in the spleen brain and intestinal mucosa as well and is due to the pigment deposited in the parasite macrophages and reticuloendothelial cells

Two types of pigments are seen in the liver as well as other organs The malarial pigment is a black iron containing substance which is specific for this disease According to Strong it can be split into a protein and hematin from which hemozoin is derived It is not found in the circulation in any other disease although a similar pigment may be found extravascularly in schistosomiasis and melanotic tumors Because it does not give a reaction for iron it has been thought by some to be free of iron The other pigment is hemosiderin which is found in other hemolytic conditions and in hemochromatosis

Microscopically the Kupffer cells are seen packed with the black malarial pigment while the parenchymatous cells show yellowish granules of hemosiderin Parasites may be seen within the Kupffer cells or within small venules which may be plugged by them The congestion may be due to this venous plugging Centrolobular necrosis has been emphasized by Andrews who pointed out that these changes are similar to the lesions seen in congestive heart failure and Chiari s syndrome and may be due to anoxia The anoxia is due to the anemia and obstruction of the venous drainage from the organ Less commonly necrosis may be seen in the periportal areas Cloudy swelling and vacuolization of parenchymal cells may be present

Cirrhosis

In chronic recurring malaria increased connective tissue is found in the liver The frequent association of malaria with cirrhosis of the liver has led to the question of a cause and effect relationship However in the tropics where this association is most commonly seen malnutrition may play the crucial role in the pathogenesis of cirrhosis Thus we are again faced with the problem of multiple causation in the genesis of liver disease While it is generally agreed that when cirrhosis is present some other causative factor has been operating it is nevertheless true that malaria per se can and does produce anatomical changes in the liver and therefore would play a contributing factor The repeated hemolysis in chronic recurring malaria along with pigment deposition in the liver may lead to cirrhotic changes as seen in other cases of pigment cirrhosis

Pathology—Summary

Liver—moderately enlarged
color—slate gray blackish due to
Pigments
1 malarial pigment—specific black iron containing
2 hemosiderin
Microscopically
Kupffer cells—contain malarial pigment and parasites
Parenchymatous cells—contain hemosiderin
centrolobular necrosis—due to anoxia caused by anemia and venous plugging by parasites
periportal necrosis—less common
cloudy swelling and vacuolization
Cirrhosis
is common in patients with chronic recurrent malaria
malnutrition is a most important factor in its genesis

Clinical and Laboratory Features (Spontaneous Disease)

During World War II there has been an increased impetus in the study of the effect of malaria on the liver Kern and Norris from a study of 100 cases of *Plasmodium vivax* and *P falciparum* infection concluded that "demonstrable involvement of the liver occurs in the majority of all cases of malaria and in all stages of disease including the earliest acute attack," and that "the incidence is far greater than is commonly realized"

The clinical evidence of hepatic involvement consists of nausea vomiting upper abdominal pain jaundice hepatic enlargement and tenderness While the first three may be due to the general toxemia the last three are more likely due to the specific hepatic origin

Jaundice is however, an uncommon finding in malaria it may be due to hemolysis and may not be hepatogenous Hills found an elevated icteric index in 24 of 8 837 patients examined This was four times (0 27%) commoner in falciparum than vivax malaria This rarity of icterus is not confirmed by other reports (see below) While some of these cases of jaundice are probably on a hemolytic basis the degree of icterus and presence of bile in the urine point to hepatocellular origin in others The hemolytic component of jaundice in malaria is graphically illustrated by Strong (Fig 41), in which it is shown that the serum bilirubin rises as the erythrocyte count falls However, even in this illustrative case a hepatic factor was undoubtedly involved since a serum bilirubin of 8 mg % could hardly be produced by a hemolysis so slight as to produce an erythrocyte count of slightly under 4 0 million

Milanes and co workers reported a case of hepatogenous jaundice in a patient with malaria In spite of the thorough study of the case including liver biopsy, they were unable to decide whether some other factor besides malaria contributed to its genesis While the authors are inclined to the latter view, this does not appear to be warranted by the facts at hand

The pathogenesis of jaundice in this disease is undoubtedly due to a combination of hemolysis and hepatic injury The latter may be caused by direct toxic effect of the parasite by the anemia, by venous obstruction caused by parasites in the liver and by increased demand on the liver from the increased pigment metabolism

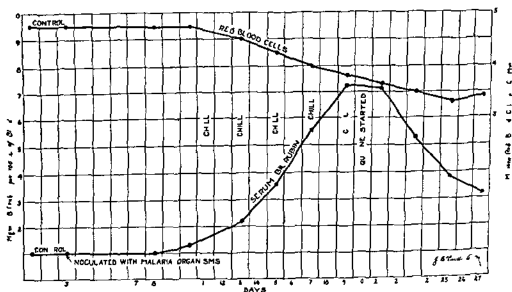


Fig 41 This graph demonstrates the rise of serum bilirubin as the red blood cells fall in a patient with malarial paroxysm (From Richard P Strong *Stitt's Diagnosis Prevention and Treatment of Tropical Diseases* The Blakiston Company Philadelphia Vol 1 1944)

The liver is frequently enlarged and at times tender. In the 4 cases with jaundice analyzed by Hills the liver was enlarged in 10; in three of these the liver was tender. The spleen was enlarged in 13 of these patients. The liver may be enlarged and tender even in the absence of clinical jaundice.

Laboratory tests have been utilized by numerous workers to determine the frequency and degree of hepatic dysfunction in malaria. Mirsky and co-workers found the cephalin-cholesterol flocculation test abnormal in 10 patients with malaria. Schneider and Shallenberger made laboratory determinations on 250 patients with malaria. The tests were done immediately after the patient became afebrile under Atabrine (quinacrine hydrochloride) therapy and included icteric index, bromsulphalein retention, hippuric acid excretion, prothrombin time, total proteins and albumin-globulin ratio. About one third of the patients studied showed several abnormal liver function tests. The cephalin-cholesterol test was positive in about two thirds of the patients. Cholesterol ester decrease was found in only 6% of 112 patients tested. It is interesting to note that the icteric index was elevated in 31% of cases. This contradicts the impression of the rarity of this finding gained from other reports (Hills 1946). A similar study by Lippincott et al (1945) in 317 patients with relapsing vivax malaria revealed 8 % with positive flocculation tests and 16% showed an elevated icteric index. The serum phosphatase and cholesterol levels remained normal. Urine urobilinogen excretion was increased.

Hemoglobinuria is frequently seen in patients with jaundice and is an index of rapid hemolysis.

Therapeutic Malaria

The use of induction hyperthermia in patients with neurosyphilis by intravenous inoculation with Plasmodium malariae offers a rare opportunity for study of this disease. Liver function studies were done by a number of workers on such patients with the conclusion that liver injury almost invariably takes place. Read, Kaplan, Becker and Boyd found hepatic enlargement in 74 of 300 patients (24.7%). Splenomegaly was more frequent in over 80%. Anorexia, nausea, vomiting, abdominal pain and edema were encountered in a significant number of patients. Jaundice was found in 22 of these patients and appeared to be commoner in vivax malaria.

Liver Function Tests

Abnormalities in liver function have been noted previously by Fong (1937), Kroll (1940) and Kirby and Bunker (19 5). More recently Gutman and co-workers found the cephalin-cholesterol flocculation strongly positive in therapeutic malaria. This was accompanied by alteration of serum protein, an increase of the gamma globulin and decrease of the albumin. Fredricks and Hoffman found bromsulphalein retention and positive cephalin-cholesterol flocculation tests in all of 31 cases. Nearly half of them showed hyperbilirubinemia and hyperurobilinogenuria. Similar observations were made by Lippincott and associates (1946) and Glenn and co-workers (1946).

Atabrine Effect on Liver

Since Atabrine (quinacrine hydrochloride) was used during or prior to studies on spontaneous malaria, an untoward effect of the drug on the liver has to be ruled out. There is no evidence that Atabrine by itself produced disturbed liver function. McCorkle utilized the hippuric acid excretion test on 55 patients receiving Atabrine and quinine. Eight of these showed initially a slight decrease of sodium benzoate excretion but this later returned to normal while the patients continued with Atabrine therapy. Butt and co-workers found no significant toxic effect on the liver from this drug in 50 patients. They used the following tests: bromsulphalein excretion, prothrombin time and serum bilirubin determinations.

Duration of Liver Dysfunction

How permanent or transient is the hepatic injury resulting from malaria? This question is of importance in spontaneous malaria, but especially important when it is used as a *therapeutic agent*. All evidence accumulated points to the transient character and reversi

bility of this process All observers agree that in both therapeutic and spontaneous malaria, *the hepatic function gradually returns to normal* I have done liver function studies in over 100 patients who had repeated malarial paroxysms (as many as 12 attacks) but were clinically well at the time of the studies The tests utilized were the bromsulphalein excretion hippuric acid excretion intravenous glucose tolerance cephalin cholesterol flocculation and serum bilirubin The results were almost uniformly in the normal range except for an occasional 2 plus cephalin cholesterol flocculation test and an occasional slight retention of bromsulphalein

Significance of Liver Dysfunction

The importance to the clinician of the above evidence is threefold

1 Since malaria does damage the liver therapeutic malaria should not be utilized until liver function tests are done and found to be normal It would be hazardous to use this hepatotoxic therapeutic agent in a patient with considerable liver damage

2 In the acute stage of the disease (both spontaneous and induced) measures should be taken to protect the liver This means an assurance of adequate proteins vitamins and carbohydrates If this cannot be supplied orally parental administration should be insisted upon

3 Although the damage to liver is transient in most cases it is conceivable that spontaneous malaria in a patient with pre existent liver injury may result in permanent aggravation of the latter Therefore it is imperative to study the patient from this point of view during convalescence

Spontaneous Malaria—Summary

Clinical Features

Nausea, anorexia, vomiting upper abdominal pain hepatic enlargement and tenderness

Jaundice

Hemolytic (prehepatic)

Parenchymatous (hepatic)

Laboratory Features

Flocculation tests—positive

Serum bilirubin—elevated

Gamma globulin—elevated

Cholesterol ester decrease—uncommon

B.S P retention—mild

Urobilinogenuria

Hemoglobinuria—occasionally

Therapeutic Malaria—Summary

Clinical and laboratory features similar to above

Effect of Atabrine on Liver

No evidence of toxic effect

Hepatic Injury is Transient

Clinical Implications

1. **Do liver function tests before therapeutic malaria and if abnormal do not use this therapy**
2. **Good nutrition during spontaneous or therapeutic malaria**
3. **Check liver function during convalescence**

34—Infection of the Liver with Metazoa

Clonorchiasis

Clonorchiasis (distomiasis) is caused by infestation with the liver fluke Clonorchis sinensis The disease is common in Asia and is especially important to us because of its abundance in Southern Korea It is also common in China Indo China Formosa and Japan *Man acquires the infection by eating* raw or insufficiently cooked fish—a custom common in the Orient Infestation with this parasite can be expected in the United States in returning military personnel I have seen ova of Clonorchis sinensis in the stools of two German refugees in Chicago who resided for a time and acquired the infection in China (Shanghai and Canton) Augustine and Isenberg and Edelman and Spingarn have made similar observations in Boston and New York

The first intermediate host is a snail A species of snail—Bulimus tentaculatus—present in the Great Lakes region is thought capable of acting as a host One must therefore be on guard for possible transmission of the disease in the United States

Life Cycle of the Parasite

The ovum has to be ingested by a snail There the egg hatches and the miracidium develops into a sporocyst This develops into rediae and these in turn develop into cercariae These must enter the body of a fish where they become encysted as metacercariae When the fish is ingested by man the metacercariae become excysted in the duodenum They enter the bile ducts where they grow to maturity The habitat of these parasites is in the bile ducts instead of the venous system of the liver as is the case with the Schistosomes

Distribution and Life Cycle—Summary

Distribution

- **China Japan Indo China Formosa Southern Korea**

Life Cycle of Liver Fluke

- **Ovum excreted in feces**
- **Ingested by snail**
  - **Egg hatches → miracidium → sporocyst → rediae → cercariae**
- **Enters body of fish and encysted as metacercariae**
- **Ingested by man with raw or poorly cooked fish**
  - **Metacercariae excysted in duodenum → enter bile ducts (here they grow to maturity) → deposit ova → ova excreted in feces → (cycle begins over again)**

Pathology

The fluke by its presence in the bile passages sets up an inflammatory process there and in the surrounding tissue Since the smaller intrahepatic bile duct may become involved a periportal inflammation and fibrosis may be expected The extent of the pathological changes depends on the severity of the infestation Although cirrhosis is assumed to be the eventual lesion in severe and prolonged cases this can be disputed in the liver fluke infestation as it is with respect to the blood fluke (Schistosomiasis)

Hoeppli studied the pathology of 66 Chinese with Clonorchis sinensis infection who died from other causes The infection was light to moderate in all but one case As is to be expected from the localization of the parasite the larger bile ducts showed dilatation thickening of their walls and hyperplasia of glandular structure Multiplication of bile ducts has also been noted Only two cases of cirrhosis were found in this group and only one of Laennec s type Since the infection in these individuals was not heavy and since they died from accidental causes the possibility exists that cirrhosis would be commoner in more advanced disease The mildness of the infection in this group of patients is further emphasized by the lack of symptoms The commonest histologic change was the increase of periportal connective tissue eosinophilic infiltration and fatty changes The latter was commonest in the center of the lobule In five cases there was increased fibrous tissue around the central vein and in four cases thickening and hyalinization of the intima of small arteries

Multiplication of the parasite in the bile ducts has resulted in their obstruction Some have referred to the development of a hyperplastic cholangitis Such changes should have a tendency to produce biliary rather than portal cirrhosis

The possible relationship of this disease to primary carcinoma of the liver has been discussed in another section Suffice it to say here that if *clonorchiasis predisposes to* primary hepatic carcinoma it should be a cholangioma and not a hepatoma in view of the localization of the parasite

Pathological changes in the pancreas are also occasionally found owing to localization of the parasite in the pancreatic duct

Pathology—Summary

Process involves bile ducts and adjacent areas
- **Dilatation of bile ducts**
- **Thickening of bile duct walls**
- **Hyperplasia of glandular structures**
- **Multiplication of bile ducts**
- **Periportal fibrosis and eosinophilic infiltration**
- **Fatty changes, principally centrolobular**

Cirrhosis
- **Portal type (?) due to organism**
- **Biliary cirrhosis is more likely because of involvement of bile ducts**

Clinical Features

Infestation may be present for a long time without symptoms or producing only mild symptoms The two patients I observed had mild dyspepsia and vague abdominal pains Their nutritional state was excellent Bercovitz who reviewed the clinical manifestations in a large group of patients in Korea emphasized the chronicity and benignity of the disease Chills and fever were absent In addition to the mild abdominal pain some patients complained of hepatic enlargement Night blindness was one of the symptoms this may have been due to defective vitamin A absorption or utilization Of 10 typical patients seven had hepatic enlargement and five had ascites but only two were icteric In the terminal stage with anasarca emaciation is undoubtedly complicated by severe malnutrition primary or secondary

Clinical studies of the disease in Japan resulted in a classification of the following stages (1) a mild type without symptoms or mild symptoms (2) severe infection accompanied by diarrhea edema and enlargement of the liver and (3) severe type with symptoms as found in (2), but aggravated by hepatic cirrhosis

Clinical Features—Summary

May be asymptomatic or mild
- **Dyspepsia**
- **Vague abdominal pain**
- **Hepatic enlargement**
- **Night blindness (poor vitamin A absorption)**
- **Ascites and icterus—occasionally**

Terminal—grave symptoms complicated by malnutrition

Laboratory Findings

Leukocytosis and eosinophilia *are frequent* findings Bercovitz found a leukocyte count up to 31 000 and an eosinophil level up to 48% Higher eosinophil levels have been reported The hemoglobin may be slightly reduced

The characteristic ovum may be found in the stools or in the duodenum by biliary drainage

Laboratory Findings—Summary

Leukocytosis eosinophilia mild anemia

Ovum found in stools or duodenal contents

Diagnosis

The diagnosis depends on finding *the ovum* In the presence of eosinophilia other *parasitic* infestations may be suspected The differentiation can be made only by parasitological means It should be kept in mind as a possible cause of jaundice in persons who have *lived in* the Orient

Treatment

The *treatment* of this disease is unsatisfactory gentian violet in enteric coated tablets 0 06 gm (1 grain) three times daily before meals for 20 to 30 days is usually given Intraduodenal instillation and *intravenous* administration of gentian violet *has also* been recommended The latter is given in 1% solu

tion o cc for first dose followed by 30 cc three days later Antimony compounds have been used as in schistosomiasis

Oral treatment with two courses of gentian violet has apparently cleared one of our cases of ova Other cases are resistant to gentian violet as well as Fuadin (stibophen) If the patient is not heavily infected and is secure from reinfection as in the United States the parasite is spontaneously eliminated within several years

Bercovitz used biliary drainage by duodenal tube and reported some measure of success in eliminating the ova

Treatment—Summary

Treatment unsatisfactory
- **Gentian violet**
  - **Enteric coated tablets 0 06 gm (1 grain) three times daily before meals**
  - **Intraduodenal instillation**
  - **Intravenous 1% solution 20 cc 1st dose 30 cc three days later**
- **Antimony compounds**
  - **Used as for schistosomiasis**

ECHINOCOCCUS (HYDATID) CYSTS

Echinococcosis (hydatid or Echinococcus disease) is caused by a species of tapeworm (cestode) Echinococcus granulosa (Taenia echinococcus) and produces cysts in various organs predominantly in the liver and lungs

Parasite and Life Cycle

The adult worm lives in the small intestine of dogs or other carnivores the wolf the jackal and probably the cat These are the definitive hosts Structurally the helminth is much like a tapeworm but is very short measuring only 3 to 8 mm in length The tapeworm form is found only in dogs or other definitive host Ova are passed by the definitive ho t and are picked up by the intermediate hosts cattle sheep hogs and many other mammal including man The ova are ingested in contaminated food or water In man and other intermediate hosts only the cystic form is present Man usually becomes infected by close association with infected dogs This animal becomes re infected from ingestion of the viscera of infected sheep

Parasite and Life Cycle—Summary

Ecchinococcus granulosa (Taenia Ecchinococcus)
- **Structurally—adult helminth is very short tapeworm 3-8 mm long**
- **Definitive host**
  - **Dog or other carnivorous animal—in intestinal tract**
- **Intermediate host**
  - **Cattle sheep hogs and man**
  - **Only cystic form is present in these**

Geographic Distribution Incidence

Because of the life cycle of the parasite the disease is commonest in countries where sheep are raised Thus the incidence in Australia and New Zealand is very high where there are 13 to 15 sheep per capita and in Ireland where there are two sheep per capita (Godfrey) Other countries where it is commonly seen are Algiers Bulgaria Rumania Switzerland France Austria Northern Italy and Russia Its incidence has become significant in Argentina and Uruguay It occurs locally in England China Japan and the Philippine Islands In the United States and Canada the disease is rare and has been decreasing in frequency since 19 4 when immigration was reduced Magath added 10 cases to 48 reported since 1908 In 95% the disease occurred in immigrants or was acquired outside of the United States and Canada Only four of these were acquired in Canada and nineteen in the United States In this country the disease has apparently been acquired in Maryland Missouri Indiana New York Arkansas and Northern Minnesota

In most countries the incidence of the disease depends on the number of sheep per capita and the degree of infection in dogs The infection then most frequently occurs in children because of their closer contact with dogs In the United States dogs rarely harbor the organism and adults are the ones most frequently infected This situation is explained by Riley as being due to a life cycle of the parasite in wild animals moose and wolves hogs and man being the accidental secondary host

Geographic Distribution—Incidence

Most common in sheep raising countries
- Australia and New Zealand—very high
- Iceland—next in frequency

Seen in
- Algiers, Bulgaria Rumania, Switzerland France Austria Northern Italy and Russia also Argentina, Uruguay England Japan and the Philippine Islands
- United States and Canada rare and decreasing usually in immigrants or acquired outside of the United States

Pathology

The ingested ovum loses its resistant chitinous envelope by gastric digestion The liberated ovum attaches itself by hooklets to the stomach or intestine burrows through the wall into a tributary of the portal veins and into the liver This organ is by far the one most commonly involved The liver was involved in 56 of Dungal s 60 cases in 61% of Douglas s 140 cases and 76% of Rose and Culbertson s collected cases The liver was involved in 74% of the North American cases The organ next in frequency of involvement is the lung but the kidneys spleen intestinal wall and peritoneum as well as the brain or almost any organ may be involved The right lobe of the liver is most frequently involved (67% Dungal) while the left lobe was involved in 12 5% and both lobes in 1 5% of his cases The hepatic cysts are usually single but may be multiple (as many as four or more) The size varies widely from the size of a pea to 50 cm in diameter and may contain 16 liters of fluid (Dungal)

The cyst may become infected and then turn into an abscess In its uncomplicated state the fluid is clear but occasionally may be brownish from hemorrhage The cyst wall consists of three layers The outer layer is a fibrous layer formed by the host called the pericyst or adventitia The inner or germinal layer (endocyst) is a protoplasmic matrix containing many nuclei and produces numerous bud like processes which become vesicular and are termed brood capsules These in turn give rise to scolices with the hooklets and suckers The middle layer or outer layer of the true cyst is a thick laminated capsule The brood capsules may drop off from the wall of the cyst and settle as hydatid sand Daughter cysts may develop from invagination of the wall of the enlarging cyst or more usually from the brood capsules or scolices

The expanding cyst produces pressure necrosis of the surrounding hepatic parenchyma and by its size and location may compress the bile ducts

Pathology—Summary

Ovum loses its resistant envelope by gastric digestion
- Burrows through intestinal wall—
- Into tributary of portal vein—
- Reaches liver

Liver
- Commonest organ involved right lobe most frequently

Lungs
- Next most commonly involved kidneys, spleen nearly any organ may be involved

Cyst
- Size from pea to 50 cm in diameter
- Contents
  - Clear
  - Hemorrhagic or
  - Purulent
- Wall consists of three layers
  1. Outer fibrous layer pericyst (adventitia)
  2. Inner germinal layer (endocyst)
  3. Middle layer thick laminated capsule
- Daughter cysts from wall of cyst or from brood capsules

Pressure necrosis surrounding parenchyma
- May compress bile duct

Clinical Features

Hepatic hydatid cyst is compatible with good health and may be asymptomatic (Douglas) It may be discovered accidentally on routine examination when it reaches sufficient size If it is of sufficient size some dragging sensation in the upper abdomen may be complained of or there may be fulness nausea or epigastric pressure

The unilobar hepatic enlargement suggests a hepatic neoplasm On percussion over the area the hydatid thrill may be elicited While this has in the past been considered a diagnostic sign Douglas doubts its value because of its rarity and lack of specificity Fluctuation can sometimes be elicited over the cyst but because of the great tension within it this is uncommon The round smooth cystic mass

may be occasionally palpated on the inferior surface of the liver

Jaundice may occur because of compression of the large hepatic ducts in the portahepatica or because of concomitant cirrhosis which is probably coincidental Jaundice may also occur because of intrabiliary rupture of the cyst The rupture may occur into one of the large hepatic ducts or into the gallbladder The spillage of the hydatid material into the biliary tree results in symptoms of cholecystitis and biliary colic (Atlas & Kamenear) The jaundice is therefore of the post hepatic type

Intraperitoneal rupture of the cyst is a catastrophic complication The symptoms resemble an acute abdomen due to rupture of a *hollow viscus and are usually diagnosed as such* The hydatid anaphylactic reactions have been exaggerated in importance according to Douglas In the first stage there is a shock like picture with hypotension and tachycardia followed by the second stage with urticaria and pruritus The great danger of rupture is the implantation in the peritoneal cavity with formation of myriad cysts which makes the ultimate prognosis extremely poor

Rupture of the cyst into the gastrointestinal tract or into the biliary tract may result in spontaneous cure

Infection of the cyst may occur either by the hematogenous route or through bile ducts Suppuration due to pyogenic organisms results in death of the parasite and the cyst turns into an abscess cavity bringing in its trail symptoms of sepsis These include chills fever pain tenderness leukocytosis and wasting

Clinical Features—Summary

May be asymptomatic or dragging sensation in upper abdomen fulness nausea or pressure
Unilobar cyst may suggest a neoplasm
Hydatid thrill } Rare
Fluctuation }
Jaundice—due to compression of bile ducts
Intrabiliary rupture—produce symptoms of biliary colic
Intraperitoneal rupture
Catastrophic symptoms
Shock urticaria, pruritus
Rupture of cyst into gastrointestinal or biliary tract—spontaneous cure
Infection
With symptoms and signs of sepsis

Laboratory Findings

Eosinophilia is present in 20% to 25% of cases, but may not be marked Anemia and leukocytosis may occur if complications have occurred

X ray may be of distinct help in the diagnosis if calcification of the cyst wall occurs The cyst wall may be sufficiently dense so that without calcification its presence may be detected The elevation of the right diaphragm in cysts of the right lobe at least calls attention to the site of the pathology Finding of cysts in the lungs may suggest their presence in the liver

Diagnosis

The diagnosis depends upon several immunological reactions

1 Cutaneous test (*Casoni s reaction*) consists of injecting hydatid fluid subcutaneously and this is followed by a wheal and flare The reaction may be immediate in 10 to 20 minutes a wheal develops surrounded by a zone of erythema A delayed reaction in 10 to 12 hours consists of a large area of erythema (5 to 6 inches) lasting 24 to 72 hours Because of the difficulty of obtaining the hydatid fluid in this country Rose and Culbertson proposed the use of fluid from cysts of rabbit infected with Cysticercus pisiformis (dog tapeworm) This material was used in 14 patients with hydatid cysts of the liver and all gave positive reactions stronger than with hydatid fluid This substitute antigen can also be utilized in the complement fixation test

2 The complement fixation test depends on the development of circulating antibodies in the blood and is performed similarly to the Wassermann test Both of these tests should be done when possible The complement fixation

test should be done first lest subcutaneous injection of even the minute amount of antigen may produce circulating antibodies and consequently produce a false positive complement fixation test

3 A precipitin test is recommended by Godfrey who considers it positive in 65% of cases

The finding of scolices in the sputum gastric contents or stools may occasionally be possible when the cysts rupture into these channels Aspiration of the cyst is mentioned only to be condemned This procedure may result in a leak and widespread dissemination of the cysts and a fatal outcome

The clinical picture of a smooth cystic mass in the liver of a patient from an area where the disease is endemic plus eosinophilia and suggestive roentgen findings demands the immunological tests described above The differential diagnosis consists of differentiating the hydatid cyst from other causes of eosinophilia other cysts or tumors of the liver liver abscess granulomas of the liver such as gummas and tuberculomas cirrhosis and subphrenic abscess

Laboratory Findings—Summary

Eosinophilia in 20% to 25% of cases

X ray

- **Calcification of cyst wall**
- **Elevation of right diaphragm**
- **Cysts of lungs**

Diagnostic tests

1. **Cutaneous test (Casoni s reaction)**
2. **Complement fixation test**
3. **Precipitin test**
4. **Finding of scolices in sputum gastric contents or stools**

Prognosis and Treatment

Solitary uncomplicated hydatid cyst of the liver is compatible with normal existence Its expanding size may result in interference with functions of adjacent organs and pressure destruction of significant amounts of hepatic parenchyma The greatest danger to the host is from complications infection and especially rupture into the peritoneum

Treatment is necessary to prevent this catastrophe and this consists of surgery No chemotherapy has been found effective Complete extirpation is laborious and frequently impossible The procedure of choice therefore consists of sterilizing the cyst cavity and its contents by means of 1% formalin and alcohol The contents are evacuated by aspiration This should be done cautiously to prevent contamination of the peritoneum The cyst cavity is closed without drainage (Douglas)

Prophylaxis as in other parasitic diseases, is of utmost importance and is quite effective as the experience in Iceland demonstrates (Dungal) In that country infestation in patients under 20 had dwindled to practically zero while the older population is still heavily parasitized This was accomplished by public health education slaughtering of sheep in restricted areas so that dogs cannot ingest their viscera and administration of an anthelmintic once a year to every dog in the country

Schistosomiasis

Schistosomiasis or bilharziasis is a disease caused by the infestation of a blood fluke Three species of Schistosoma are known to produce human infestation S haematobium S mansoni and S japonicum the last two are of greater importance in the present discussion because of their predilection for the liver

Life Cycle of the Parasite

These trematodes have characteristic large ova S mansoni has a lateral spine and is the largest of the three (175 by 45 by 68 microns) S japonicum is the smallest and has an inconspicuous rudimentary spine S haematobium has a terminal spine

When the ovum is excreted in the feces (S mansoni and S japonicum) or in the urine (S haematobium) it finds its way into water ruptures and liberates a miracidium The miracidium penetrates the body of a suitable snail where after a period of one or two months cercariae develop and emerge from the snail Cercariae are viable for 72 hours and swim about freely The cercariae upon drying on the skin of bathers penetrate the skin and enter the lymphatics From there they are carried to the capillaries of the lungs and then to the systemic circulation Finally they lodge in the mesenteric and portal vein There they

develop into mature worms and lay eggs in the liver and colon The S haematobium lodges in the veins of the urinary bladder These eggs break out of the wall of the colon or bladder and are excreted the cycle then starts over again

Following is a schematic presentation of the life cycle

Ovum in water —(l b rat)→ miracidium —(rs)→ snail —(m th)→ cercariae —( )→ human lymphatics → pulmonary capillaries → general circulation → mesenteric and portal veins → adult worm —(d lops)→ ova deposited → ova excreted into water → (cycle starts over again)

Geographic Distribution

S man oni is widespread in *Puerto Rico* and Northern and Eastern South America This species as well as S haematobium is found in abundance in the Nile Valley of Egypt S japonicum i chiefly found in the Orient and Pacific Islands It is found in Japan China Formosa and the Philippines This distribution has a bearing on cases seen in the United States since many American troops became infected while bathing in infested waters around Leyte S mansoni is seen in the United States chiefly in natives of Puerto Rico

Since snails are necessary vectors in the transmission of the disease it is worth noting that two species found in the United States appear suitable for this (Shattuck) One of these was found in Louisiana and the other in the Potomac River near Washington

Distribution—Summary

S mansoni
- **Puerto Rico**
- **Northern and Eastern South America**
- **Nile Valley**

S japonicum
- **Orient, Pacific Islands**
- **Japan**
- **China**
- **Formosa**
- **Philippines**

United States cases are of
- **Puerto Rican origin or**
- **Acquired by troops in the Philippines**

Pathology and Pathogenesis

The pathologic process is initiated by deposition of ova in the lower bowel and rectum in the case of S mansoni and throughout the colon and even small intestine in the case of S japonicum S haematobium is deposited in the urinary bladder The latter usually does not produce hepatosplenic involvement The deposition of the ova in the wall and submucosa of the colon sets up a chronic inflammatory process with granulomatous formation and pseudopolyposis The ova and worms reach the portal veins from the mesenteric veins of the bowel and finally lodge in the liver

Hepatosplenic involvement is an almost constant feature in chronic schistosomiasis mansoni and japonicum The liver may be enlarged and nodular at first but later the organ may shrink from contraction of the fibrous tissue The ova are deposited in the terminal radicals of the portal vein setting up a foreign body reaction with pseudotubercle formation These may show foreign body giant cells and eosinophils Small abscesses may form around the ova The numerous ova and concomitant granulomatous reaction may obliterate the venous channels with resultant periportal fibrosis and increase in portal pressure Most writers on the subject speak of the development eventually of a portal cirrhosis or pipe stem cirrhosis The formation of the cirrhosis has been attributed not only to the mechanical irritation of the ova which would then depend entirely on the number of ova present but also to a chemical substance emanating from the parasites In this manner the cirrhosis has been explained when ova were few or absent from the liver

The theory of the pathogenesis of portal cirrhosis from schistosomiasis infestation has recently come into question Lippincott and co workers performed autopsies in two cases of S japonica infestation and found minute frank abscess and pseudo tubercle formation and localized fibrosis but no fatty changes and no evidence of developing cirrhosis Symmers (1951) summarized the pathological findings in five cases of S mansoni studied post mortem at Bellevue Hospital Only two of these showed frank cirrhosis and in these two the histology pointed to independent origin of the cirrhosis Thus the cirrhotic process was perilobular but the schistosomal granulomas were in the walls of blood vessels or among parenchymal cells One case showed passive congestion and areas of interlobular fibrosis and scattered numerous granulomas around ova The last two showed exclusively parenchymatous granulomas around ova Symmers stated that it is unlikely that an innocuous foreign body like an ovum should be productive of extensive fibrosis and cirrhosis and if the latter is present it is a result of malnutrition

This again brings up the ever recurring question in the etiology and pathogenesis of liver disease

Which of several agents are responsible for the final pathologic state? The answer to the question in this particular situation can be no more definitive than in the other instances It does seem unlikely that a localized injury such as occurs from the irritation by an ovum should produce diffuse cirrhosis On the other hand if the ova are numerous enough and interfere with blood supply their influence may become diffuse and widespread A chemical substance emanating from the parasites while unproved and unlikely has not been entirely refuted

An aid in solving this riddle would be a statistical approach If one could demonstrate as great an incidence of portal cirrhosis in livers free of Schistosoma infestation but in individuals subject to the same nutritional deficiencies the observation would favor the relegation of the parasite to an incidental role If one could further show that well nourished patients infested with this helminth showed no cirrhosis the exoneration of the Schistosoma would be complete However such evidence may never be forthcoming for the classes of population most likely to succumb to schistosomiasis are the ones most likely to subsist on suboptimum diet Heavy infestation is likely to interfere with appetite and nutrition

The association between malnutrition and schistosomiasis on the one hand and malnutrition and liver involvement on the other is contradicted by the findings of Pons In 3 Puerto Rican patients with schistosomiasis all of whom showed evidence of hepatic involvement the nutritional state was described as good in 10 fair in 10 and poor in only three Thus we must admit that the pathogenesis of cirrhosis in this disease is by no means settled and will have to await further evidence

In addition to fibrosis cirrhosis and tubercles abscesses are also found Lippincott and co workers described focal necrosis of parenchyma and minute abscess Pylephlebitic abscess with secondary bacterial infection is described by Seife and Lisa in one case

The spleen is frequently enlarged usually much more than the liver This enlargement is apparently due to the portal hypertension since few or no ova are found in this organ The absence of ova in the spleen has been attributed to their possible destruction here The changes in the spleen are not pathognomonic Two patients observed by me who had splenectomies because of an erroneous diagnosis of Banti s syndrome showed no changes in the spleen indicative of the causative agent

Pathology and Pathogenesis—Summary

Ova deposited in wall and submucosa of colon and small intestine (S japonicum)

Granuloma *formation and pseudo* polyposis

Ova reach portal vein through mesenteric vein

Ova lodge in liver

- **Liver is enlarged and may be nodular**
- **Foreign body tubercles around ova**
- **Small abscess may form these may be scattered throughout liver**
- **Fibrosis around venous channels result *in portal hypertension***

Cirrhosis has been attributed to mechanical and chemical irritation of ovum

Cirrhosis has been denied as being caused purely by the parasite and attributed rather to malnutrition

Clinical Features

The clinical features of the disease have frequently been divided into stages or types Thus reference is made to the intestinal stage or type and hepatosplenic stage or type depending upon which group of symptoms predominate Those that use the expression stage convey the idea that the intestinal stage progresses into the hepatosplenic while those that use the term type suggest one or the other set of symptoms may predominate throughout the entire course

Usually the onset of the disease is with a dermatitis at the site of penetration of the cercariae this is followed within a few days or weeks with bronchial symptoms when the organisms become lodged in the pulmonary tree This may continue for several weeks and be followed by intestinal symptoms These symptoms which may occur earlier consist of generalized or localized abdominal discomfort cramps along the course of the colon nausea vomiting tenesmus and bloody diarrhea Fever of intermittent type is present

Pons describes in detail 24 patients in the hepatosplenic stage of infestation with S mansoni This stage begins when the parasite reaches the portal circulation and deposits ova in the liver Pons subdivides this phase of the disease into two stages namely, the *first* or *active stage* in which the reaction of the host is still violent with chills and fever right upper abdominal pain marked tenderness over the liver leukocytosis and eosinophilia (up to 68%)

The *second stage* occurs late in the course of the disease In Pons patients it occurred 17 months to 30 years after the onset It is the stage of fibrosis portal hypertension and splenomegaly The patient complains of fulness after meals mild abdominal pain or discomfort and selective dyspepsia to certain foods Abdominal enlargement or an abdominal mass may be the presenting symptom A dragging sensation from an enlarged spleen may cause complaints Some bowel symptoms as described above may still be present Loss of weight dyspnea pallor edema of ankles hematemesis or melena may be present

Physical findings as well as the symptoms depend to a large extent on the severity of hepatic involvement I have seen patients who excreted ova in the stool who did not look very ill and showed only a palpable spleen and a palpable liver on physical examination

Jaundice is a rare finding The liver is usually enlarged except late in the disease when it may become smaller than normal Jones patients all showed hepatic enlargement especially the left lobe The organ is largest in the stage of greatest activity when tenderness is most marked

The spleen is frequently enlarged and may be the most conspicuous finding This along with hematemesis gives rise to an erroneous diagnosis of Banti s syndrome with useless splenectomy The spleen is freely moveable and sometimes tender

In the final stage there may be much loss of weight with edema of extremities abdominal enlargement due to ascites and splenomegaly and dilated abdominal veins While this is described as the terminal stage of the disease it is not the commonest although it is the most impressive part of the clinical evolution of the disease

Clinical Features—Summary

Intestinal Stage or Type
- **Onset with dermatitis**
- **Bronchial symptoms**
- **Intestinal symptoms**
  - **Abdominal discomfort generalized or localized**
  - **Cramps along colon**
  - **Nausea vomiting**
  - **Bloody diarrhea**
- **Fever intermittent**

Hepatosplenic Stage
- **First or active stage**
  - **Chills fever**
  - **Right upper abdominal pain**
  - **Tender liver**
  - **Leukocytosis eosinophil level up to 68%**
- **Second stage (late 17 months to 30 years after onset)**
  - **Abdominal discomfort dragging sensation**
  - **Fulness after meals**
  - **Anorexia loss of weight**
  - **Abdominal enlargement—edema**
  - **Hepatosplenic enlargement**
  - **Jaundice—rare**
  - **Hematemesis and melena**
- **Final stage**
  - **Ascites massive edema**
  - **Dilated abdominal veins**
  - **Emaciation anemia severe**

Laboratory Findings

Liver function tests were done by Lippincott and co workers on over [illegible]00 American soldiers infected with S japonicum Their data indicate that only a small minority exhibit abnormalities and these are minor This seems to substantiate the opinion that this disease per se does not produce hepatic cirrhosis The most significant deviation from normal was in bromsulphalein retention 1[illegible]% of patients showed abnormal values The icteric index was elevated in 4% of patients and the globulin fraction of the blood serum was increased in 5% These workers further found an increase in BSP retention and greater elevation of serum bilirubin after treatment with antimony compounds (Table 44)

My experience with several soldiers infested with S mansoni is similar to theirs namely that liver function tests are either normal or only slightly disturbed It should be pointed out that with progression of the process development of ascites and other clinical evidence of hepatic failure these tests are expected to become more abnormal Seife and Lisa reported

TABLE 44

Results of Initial Tests of Liver Function in Patients Infested with Schistosoma Japonica on Their Return from Overseas

Type / T t	\ m b f M	\ m l T t		Ab	m l T t
		\	P t g	\o	P tage
Globulin	175	167	95	8	5
Formol Gel	84	83	99	1	1
Icterus Index	16	155	96	7	4
Serum Bilirubin	46	31	94	15	6
Urobilinogen	85	85	100	0	0
IV Hippuric	108	103	95	5	5
Calactose	189	18	96	7	4
Bromsulfalein	45	15	88	30	1

S W Lippincott F K Paddock M C Rhees W B Hesselbrock and L D Ellerbrook Tests of Liver Function in Schistosomiasis Japonica with Particular Reference to Antimony Treatment and with Report of Two Autopsies Arch Int Med *79* 6 1947

a thymol turbidity of 17 units and an elevated alkaline phosphatase level in their case complicated by abscess

The blood count may show anemia and leukocytosis during the active stage Eosinophilia may be marked at first but a 20 to 25% eosinophil level may persist and give a clue into the diagnosis This was the situation in two of our patients that had splenectomies elsewhere without an etiologic diagnosis

Stools may contain blood and ova of the parasite can usually be demonstrated The entire stool should be sent to the laboratory and if mucus or blood is seen on the surface a smear should be made of this for it is likely to contain the ova

Sigmoidoscopic examination may reveal pseudopolyposis Even when the mucosa appears grossly normal a biopsy may reveal the presence of ova The thin piece of tissue may be spread between cover slip and slide and examined in the fresh state

Needle liver biopsy in doubtful cases may demonstrate the pseudotubercles in the liver and the finding of ova would complete the evidence

Immunological and serological tests have been employed in the diagnosis of this disease but their specificity has not been completely verified Among these should be mentioned the complement fixation test (Williams) and the intradermal test (Katzin and Most)

Laboratory Findings—Summary

Liver Function Tests
- **Mild abnormality**
- **BSP slight retention**
- **Mild hyperbilirubinemia—occasionally**
- **Globulin elevation**
  - **Increased abnormality in terminal cases**

Blood count
- **Anemia**
- **Eosinophilia**

Stools
- **Blood, gross and/or occult**
- **Ova**

Sigmoidoscopic
- **Pseudopolyposis**
- **Biopsy or rectal mucosa may reveal ovum in submucosa**

Needle Biopsy of Liver
- **Granuloma**
- **Ovum in liver tissue**

Immunological Tests
- **Complement fixation test**
- **Intradermal test**

Treatment

Prophylaxis consists of elimination of snail avoidance of contamination of bathing areas with excreta and prohibition of bathing in polluted water

In the active treatment of the disease antimony preparations are used Fuadin contains 13 6% of trivalent antimony It is available in 5 cc ampules and is administered intramuscularly 1 5 cc on the first day 3 5 cc on the second day and 5 cc every other day Previously a total of 70 cc was recommended Recently a total dose of 100 cc has been recommended by the American Public Health Service Association

Tartar emetic 0 5% (potassium antimony tartrate) is given intravenously in isotonic sodium chloride The dose is 8 cc initially increasing by 4 cc every other day until a maximum single dose of 28 cc is reached Immediate toxic effects of cough nausea and vomiting are common with this drug but it is thought to be

more effective than Fuadin A possible toxic effect on the liver has been reported by Lippincott and co workers Tarr has noted from electrocardiographic studies that antimony compounds (Fuadin and tartar emetic) produce myocardial damage Tartar emetic produced more consistent changes These effects on the liver and myocardium appear to be transient and do not preclude the use of these drugs

Treatment—Summary

Prophylactic
- **Elimination of snail**
- **Sanitation—to prevent contamination of bathing areas**
- **Prohibition of bathing in polluted areas**

Active Treatment
- **Fuadin—solution intramuscularly**
  - **1.5 cc 1st day**
  - **3.5 cc 2nd day**
  - **5 0 cc every other day**
  - **Total—100 cc**
- **Tartar Emetic intravenously**
  - **0.5% in isotonic NaCl**
    - **1st dose—8 cc**
      - **Increase by 4 cc every other day until 28 cc single dose is reached**
- **Watch for toxic reactions**
  - **On liver and myocardium These are transient and do not preclude its continued use**

35 Yellow Fever

Yellow fever is an acute infectious disease caused by a filtrable virus transmitted to man by the bite of the Aedes aegypti mosquito or related strain It is characterized pathologically by hemorrhage degeneration of the liver kidneys and myocardium and clinically by the consequences of the changes in these organs

Background

This disease has played an important role in the history and vicissitudes of civilization There is reason to believe that it originated in Africa and was brought to America by slave ships from that continent The first epidemic on this continent probably occurred in Mexico in 1648 Aggressors of old fared poorly with this disease In 1802 Napoleon s army on the Island of Haiti was destroyed by yellow fever The disease traveled north along the Mississippi River and epidemics were described in New York Philadelphia and as far north as Quebec and Nova Scotia The conquest of the disease began with the military commission in 1900 headed by Major Walter Reed and the discovery of Aedes aegypti as the vector of the disease Reed and his co workers (James Carroll Aristides Agramente and Jesse W Lazear) also demonstrated that the disease is produced by a filtrable virus This knowledge enabled Gorgas to eliminate the disease from Havana and Panama which made possible the building of the Panama Canal

Epidemiology

Types of Disease

The disease is divided into the urban rural jungle or sylvan types These varieties are chiefly dependent upon their location and to a lesser extent on some differences in vectors

Vectors

All the vectors are mosquitoes, the most important of which is the Aedes aegypti. However, the others mentioned by Shattuck are Aedes simpsoni, A. africanus, Haemagogus capricorni, and A. leucoceloenus. The mosquito transmits it from man to man. After biting a victim afflicted with the disease, the virus has to develop in the mosquito for 12 days before it can be transmitted by a bite to another individual. This is called the extrinsic incubation period. It should be pointed out that A. aegypti is found in the southeastern portion of the United States and is a potential source of an epidemic.

Host

It has been shown that primates (monkeys, baboons) are susceptible to yellow fever virus and may act as a reservoir from which the disease is carried by mosquitoes to human victims.

Geographical Distribution

The disease still occurs in Africa and South America, especially Brazil and the Amazon Basin. A major epidemic occurred in Nigeria in 1946 (Findlay). For the first time since 1905 eight cases and six deaths were reported from Panama in 1949 (Dick and Smithburn).

Etiology—Summary

Causative agent filtrable virus
Vector Mosquitos
- **Aedes aegypti**
- **Aedes africanus**
- **Aedes leucoceloenus**
- **Haemagogus capricornii**

Extrinsic incubation period (in mosquito) 12 days
Animal reservoir
- **Monkeys**
- **Baboons**

Geographic distribution
- **Aedes aegypti is found in Southeastern part of the U.S.A.**
- **Endemic in Africa, South America (esp. Brazil and Amazon Basin)**

PATHOLOGY

The virus of yellow fever has been referred to as having viscerotropic and neurotropic properties, with viscerotropic features predominating in man. However, because of the uniformity with which the liver is damaged in this disease, the virus can be properly referred to as hepatotropic or hepatotoxic. The pathologic features may be divided into the following spheres of injury: (1) hepatic, (2) renal, (3) cardiac and (4) hemorrhagic.

1. Hepatic

While the liver may not always show the most severe involvement, it is invariably affected and shows the most characteristic changes. The pathology of the liver has been ably studied and discussed by Klotz and Belt. The gross changes are negligible compared with the microscopic findings. The size of this organ remains unchanged or is slightly enlarged. The various lobes retain the same proportions as the normal organ except occasionally the right lobe is more involved than the left. The color of the liver is usually unchanged, but occasionally is greenish. Petechial subcapsular hemorrhages are occasionally observed, but these are not marked. Many of the gross color changes reported may have been due to postmortem changes or loss of blood from the liver.

Microscopically the changes in the liver are usually more extensive than in any other organ and belie its relatively normal gross appearance. The liver injury has many unusual and distinct features.

1. The involvement is diffuse, involving all the lobules.
2. There is necrosis and necrobiosis involving only the parenchymal cells.
3. The reticulum or supporting structure is spared.
4. Inflammatory exudative changes are conspicuous by their absence.
5. Midzonal accentuation of the process is noted when the entire lobule is not destroyed.

The disorganization of the hepatic parenchyma is obvious at a glance. The degenerative features have been divided into three groups:

a. Hyaline necrosis (Councilman lesion). This lesion is found in the parenchymal hepatic cells of all patients dying from yellow fever and is pathognomonic for the disease. It is an advanced stage of coagulation necrosis. The cells or parts of cells that have undergone this change assume a spherical form. They are strongly eosinophilic, highly refractive and homogeneous, hence the term "hyaline necrosis" or "hyaline bodies." Vacuoles containing fat granules may be seen within them. The hyaline necrosis may be more severe in the midzonal area of the lobule, tapering off both centrally and peripherally.

b Fatty changes Increased accumulation of lipids in the parenchymal cells is another constant characteristic in this disease This may be present in small or large droplets The latter occupy the better preserved cells while the former occupy the more damaged cells This increase in fat is not marked and severely fatty livers are unusual

c Cloudy swelling This change is also constantly seen in yellow fever It is characterized by a granular appearance of the cytoplasm and edema of the better preserved cells This is a mild and reversible degenerative change and unlike hyalin necrosis it more commonly effects the central and peripheral portion of the lobule The cloudy swelling and fatty changes account for the increased bulk of the organ despite the severe necrosis

The nuclear changes are not pathognomonic of the disease and are noted in the better preserved cells They consist of nuclear edema acidophilia chromatolysis and nuclear inclusion bodies It is of interest to point out that mitoses are rarely seen in fatal yellow fever hence it may be surmised that this hepatotoxic virus for a time destroys the regenerating ability of the liver When the patient recovers regeneration is complete and takes place without fibrosis

An interesting chemical and histological finding is the marked loss of glycogen by the parenchymal cells This glycogen depletion parallels the degree of degeneration and explains the clinical and laboratory findings described later

Other changes in the liver consist of an accumulation of granules of yellowish brown pigment in the parenchymal and Kupffer cells probably bilirubin The Kupffer cells are better preserved and do not show the extensive degeneration of the parenchymal cells They sometimes show fatty and degenerative changes but hyperplasia of these cells is noted in the presence of jaundice

2 Renal

The kidneys like the liver show degenerative but not inflammatory changes These include the entire spectrum of changes from cloudy swelling to fatty degeneration to necrosis These changes are not too well correlated with the clinical evidence of renal failure The convoluted tubules of the cortex are most severely damaged The glomeruli may show congestion Renal regeneration is apparently also complete without residua

3 Heart

This organ likewise shows degenerative non inflammatory changes The myocardial fibers in various parts of the heart may show fatty and granular degeneration and less frequently hyalin and vacuolar degeneration These changes may involve the conducting pathways as well as the myocardium The changes in this organ amply account for the cardiovascular abnormalities in the clinical picture

4 Hemorrhages

Massive hemorrhages may be found in the stomach and intestines Lesser hemorrhages may be found in the gallbladder pericardium epicardium meninges lungs and elsewhere These may be of such magnitude as to be contributory to or responsible for the patient's death

The spleen has been found to show the following changes lymphopenia with increase of mononuclear cells of reticular tissue origin degenerative changes and occasional giant cells (Klotz and Belt)

Pathology—Summary

I Liver
- Gross size—normal or slightly enlarged
  - color—usually normal or bile stained
- Right lobe occasionally more involved
- Subcapsular hemorrhages
- Microscopic
  1. Necrobiosis and necrosis of hepatic cells—diffuse or midzonal
     - a Hyaline necrosis
     - b Fatty changes
     - c Cloudy swelling
     - d Nuclear changes in either preserved cells
  2. Reticulum framework is spared
  3. Absence of inflammatory and exudative changes

II Kidney
- Degenerative changes—chiefly in convoluted tubules of cortex
  1. Cloudy swelling
  2. Fatty degeneration
  3. Necrosis
- Absence of inflammatory changes

III Heart
- Myocardial degenerative noninflammatory changes

IV Hemorrhage
- Massive—in stomach and intestines
- Smaller—in gallbladder liver per

icardium, epicardium meninges, lungs

Clinical Picture

In areas where the disease is no longer seen it is thought of as always being a very serious disease *with a fulminant* course This is not true Indeed it may be so mild as to escape the attention of even the patient Soper groups the clinical types of the disease according to severity into four groups (1) inapparent infec tion (2) abortive form running influenza like course (3) incomplete form with severe onset but without the development of serious mani festations and (4) complete form to be de scribed presently

The incubation period (intrinsic incubation period in man) is three to six days but as long as 13 days has been reported Prodromata are absent The clinical course of the disease has been divided into two phases

First Phase (phase of infection)

The onset is abrupt An apparently well per *son is transformed into a very sick one within* a few hours The initial symptoms are similar to those of many systemic infections headache malaise aching of muscles of legs and back nausea and vomiting The temperature rises *rapidly and may reach its peak within* 24 hours

The patient appears quite ill but this is not borne out by the major physical findings The skin and conjunctivae are congested There is tachycardia in keeping with the fever This phase lasts 48 to 72 hours and occasionally longer the temperature falls rapidly to a nor *mal level but the pulse rate falls more rapidly* A bradycardia of as low as 40 beats per minute develops The more rapid fall in pulse rate as compared with the temperature was described by Faget in 1875 and is referred to as Faget s sign If the pulse rate begins rising again in spite of a falling temperature a fatal outcome is to be expected

Second Phase (phase of intoxication)

This phase begins on the 3rd to [illegible] of illness and con[illegible] the diagnostic and finding[illegible] the sympto[illegible] during the first phase increase in intensity and point to grave intoxication The vomiting be- comes more severe and the temperature rises again but a relative bradycardia persists The diagnostic triad of symptoms are those ref erable to the organs and tissues involved structurally and discussed under pathology These are (1) icterus (2) hemorrhage and (3) albuminuria, oliguria and anuria

Icterus of a mild degree visible only in the conjunctivae may appear on the second day As a rule however the icterus appears later and is not intense This is surprising in view of the severe hepatic necrosis In the fulminant cases which may show almost complete de struction of hepatic parenchyma jaundice may be absent completely There can be little doubt the jaundice is of the hepatic paren chymatous type Other evidence of the pro- found liver injury will be detailed under labora tory findings

Hemorrhage of a mild degree such as epistaxis may occur in the first phase of the disease The severe gastrointestinal hemor *rhages begin later The black vomit which* is so characteristic of this disease consists of clotted and partially digested blood The gastrointestinal hemorrhage may result in exsanguination but mild hemorrhage occurs *in all clinically diagnosable* cases Petechial skin hemorrhages are not frequent or con spicuous The hemorrhagic phenomenon is secondary to the severe intoxication and the pathologic physiology resulting from hepatic failure Abdominal pain and epigastric tender ness may accompany the gastrointestinal hemorrhages

Albuminuria of a mild degree may occur in the first phase but in the second phase 3 to 4 gm per liter of urine may be excreted This is undoubtedly due to the renal damage Oliguria and anuria may occur Anuria is a most serious prognostic sign and depends more on hepatic than renal necrosis for it is never seen in the absence of severe liver injury

Other signs such as bradycardia have been mentioned Hypertension and arrhythmia and electrocardiographic changes may occur be cause of myocardial damage In spite of the neurotropic properties of the virus nervous

system signs and symptoms are few The sensorium remains clear until the end

Clinical Picture (Complete form)—Summary

Incubation period 3 to 6 days

Clinical phases

1 **Phase of infection—up to third or fifth day**
   - **Abrupt onset of headache, malaise fever nausea and vomiting**
   - **Faget s sign fall in temperature and bradycardia at end of this phase**

2 **Phase of intoxication**
   - **Above symptoms increase again**
   - **Marked toxicity**
   - **Fever with relative bradycardia**
   - **Diagnostic triad**
     - a **icterus**
     - b **hemorrhages**
     - c **albuminuria oliguria anuria**
   - **Cardiovascular signs**
     - a **bradycardia**
     - b **hypotension**
     - c **arrhythmia and electrocardiographic changes**

Laboratory Findings

Changes in blood chemistry are profound in the severely toxemic patient and mirror the hepatic failure Indeed these changes are reminiscent of those seen in the hepatectomized animal and can be termed a nonsurgical hepatectomy Hyperbilirubinuria decreased bromsulphalein excretion and decreased blood fibrinogen content has been noted in experimental yellow fever in monkeys Unfortunately there is a lack of complete liver function studies in the human disease but these changes are to be expected The bleeding tendency may be due to decreased fibrinogen and also to the fall in prothrombin level It is to be expected that the flocculation tests would also be deranged

Hypoglycemia is commonly seen and may be severe The necrotic liver cells are unable to form glycogen hence the homeostatic control of the blood sugar is lost Th administration of a large amount of glucose especially intravenously should produce hyperglycemia followed by hypoglycemia as is seen in the hepatectomized animal Acidosis and ketonuria are no noted because the patient dies too rapidly and because the liver is unable to form ketone bodies

The nonprotein nitrogen rises but this increase is due chiefly to amino acids rather than urea nitrogen This is due to the failure of liver to deaminize amino acids and synthesize urea Uric acid and creatinine do not rise appreciably—because of hepatic dysfunction—until anuria develops

Increase of *guanidine* in the blood has been noted in experimental and clinical yellow fever This has been noted in other diseases and intoxications associated with extensive hepatic necrosis The guanidine increase may be responsible for some of the symptoms such as muscular twitching and contribute to the hypoglycemia

The *urine* shows albuminuria and cylindruria, and may show bilirubinuria and urobiliginuria

The *blood* may show *hemoconcentration* during the shock like phase or anemia from hemorrhage the leukocytes drop and progressive leukopenia develop reaching the lowest point at the end of the first week Coagulation time is prolonged

Bacteriologic and serologic tests are of course the most reliable diagnostic tests *Isolation of the virus* from the blood may be possible up to the third day of illness by injection into a susceptible animal The mouse protection test is negative at first becomes positive later and is evidence of development of specific immune bodies and hence the disease The complement fixation test is specific except for false positives in Wassermann fast sera It becomes positive in only a small proportion of human sera after yellow fever vaccination

Histologic examination of liver tissue can yield a positive diagnosis but this procedure cannot be done safely antemortem in this disease The disturbance in blood coagulation and the bleeding tendency would preclude needle biopsy in the living patient

Laboratory Findings—Summary

Hepatic derangement

Hyperbilirubinemia

icardium, epicardium meninges, lungs

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Other signs such as bradycardia have been mentioned Hypertension and arrhythmia and electrocardiographic changes may occur because of myocardial damage In spite of the virus nervous neurotropic properties of the virus

The injection of this attenuated virus produces only mild discomfort in man. The development of hepatitis accompanying the use of this virus is discussed under Viral Hepatitis. This hazard has been eliminated with the elimination of human sera from the vaccine.

Prognosis

The mortality from yellow fever has been exaggerated because of failure to take into consideration the mild forms of the disease. The mortality in the severe cases is undoubtedly high. The outcome of a given case is unpredictable and the prognosis therefore should be guarded. The following manifestations are considered of serious omen: hyperpyrexia, hematemesis, melena, extreme prostration, anuria and peptonuria. When death occurs it most commonly occurs in the first week, as demonstrated in 187 cases cited by Strong; 163 patients died in the first nine days and only 24 from the 10th to the 24th day. Fifty two patients died on the sixth day—by far the largest number. The cause of death requires no elaboration when one keeps in mind the pathology of the disease.

Treatment

The prophylaxis of yellow fever is all the more important since there is no adequate active treatment of the disease.

> The disease causes itself or kills in spite of any and every kind of treatment. —Sinval Lins

Serum treatment has been tried unsuccessfully. Apparently the intracellular virus cannot be eradicated by the immune bodies thus administered.

General nursing care and bed rest are of course imperative. During the stage of intoxication food is withheld but fruit juices and sweetened drinks are administered. Intravenous fluids may have to be given if vomiting is troublesome. Antipyretics that have a depressant action should not be administered.

The administration of calcium gluconate and lactate intravenously has been advised to combat the high guanidine content of the blood. Vitamin K has been advised but with massive destruction of liver parenchyma its effectiveness is doubtful.

Prophylaxis—Summary

17 D virus vaccine
- **Attenuated by growth on chick embryo for three years**
- **Immune bodies for at least five years**

Elimination of mosquito

Prognosis

Poor in full blown case
Serious omens
- **Hyperpyrexia**
- **Hematemesis**
- **Melena**
- **Extreme prostration**
- **Anuria**
- **Peptonuria**

Death commonly in first nine days

Treatment

Symptomatic supportive
Calcium gluconate, lactate I.V.

B S P clearance decreased
Fibrinogen decreased
Prothrombin decreased
Flocculation tests positive
Hypoglycemia—Aminoacidemia
Guanidine in blood increased
Bilirubinuria
Urobilinogenuria
Tyrosinuria

Renal derangement
Azotemia N P.N increased
Urea nitrogen may be decreased because of hepatic necrosis
Albuminuria
Cylindruria
Oliguria and anuria

Blood shows
Hemoconcentration during shock
Anemia due to hemorrhage
Leukopenia
Coagulation prolonged

Bacteriologic and serologic tests
Animal inoculation
Viremia up to third day
Manse protection test
Complement fixation test

Diagnosis

In the typical case in the proper geographic location a clinical diagnosis is not only possible but should not be too difficult The abrupt onset with the severe prostration headache albuminuria jaundice the saddleback fever and Faget s sign are quite typical The blood chemical changes and progressive leukopenia are also characteristic The final confirmation depends upon (1) isolation of the virus (2) detection of antibodies in the blood (mouse protection test) and (3) positive complement fixation

Differential diagnosis from other systemic infections involving the liver may be difficult in the atypical cases The confusion with Weil s disease is so likely that Noguchi thought that Leptospira icterohemorrhagiae is the cause of yellow fever In Weil s disease chemical evidence of liver failure is not so profound but the icterus is likely to be deeper meningitic signs are common and there is leukocytosis The demonstration of the spirochete in the blood and/or urine clinches the diagnosis Other diseases confused with yellow fever are relapsing fever malaria and other forms of acute yellow atrophy due to either poisons or viral hepatitis

Diagnosis—Summary

Depends on
1 abrupt onset
2 severe prostration
3 headache
4 albuminuria
5 jaundice
6 ' saddle back fever
7 Faget s sign
8 leukopenia progressive
9 bacteriological immunologic tests

Differential Diagnosis
1 Weil s disease
2 Relapsing fever
3 Malaria
4 Viral heaptitis
5 Toxic hepatic necrosis

Prophylaxis

This consists of eliminating the mosquito which is a vector and the use of vaccines in epidemic areas The elimination of the mosquito by sanitary measures has reduced the terrifying epidemic proportions of this disease but has not eliminated the disease entirely

Several methods have been tried to produce a satisfactory vaccine for this disease The completely inactivated virus does not produce immunity Vaccine 17 D is the most commonly used material and consists of virus attenuated by culture in vitro on chick embryo for three years This method of preparation apparently destroys the viscerotropic properties of the virus but it retains its neurotropic properties This is demonstrated by production of encephalitis in monkeys after intracerebral injection It does not produce serious illness in man 0 5 cc of the virus diluted 1 10 in normal saline injected subcutaneously results in satisfactory immunity Antibodies appear within ten days and immunity has been shown to be present as long as five years after vaccination hence revaccination is unnecessary at least for that period of time

and co workers found hepatomegaly in 27% but splenomegaly in 71% of 96 cases In the series from the Mayo Clinic (Stevens et al) hepatomegaly was observed in 18% and splenomegaly in 43% of cases In Wechsler's large series (556 cases) 17% had hepatomegaly and twice that many had splenomegaly

The *nausea* and *anorexia* that frequently accompany this disease may also be due to the hepatic involvement The prolonged asthenia which may last for weeks or months is very likely attributable to the residual hepatitis

Evidence of Chronic Hepatitis

That acute hepatitis is part and parcel of the clinical and laboratory pattern of infectious mononucleosis is well established The next question to be answered is Can this form of hepatitis be followed by chronic hepatitis and eventually cirrhosis? The observations of Watson Johnson Kahn and Stone in this regard are both interesting and suggestive Of 51 students who were asymptomatic but had laboratory evidence of subclinical infectious mononucleosis 33 showed an elevated thymol turbidity and 15 positive cephalin cholesterol flocculation Not only did they find evidence of hepatitis in the subclinical form of the disease but evidence of chronicity was suggested in seven of these students by positive thymol turbidity 22 months after the original study In the series of patients followed by Bennett and co workers four patients showed abnormal tests for five to nine months and one for as long as 31 month The prolonged icterus reported by Abrams has been mentioned In the DeMarsh and Alt series some tests remained positive for as long as four and a half years

The next question of utmost clinical importance is whether this hepatitis can eventually lead to cirrhosis The evidence for this is meager but Leibowitz and Brody reported a suggestive case A young male patient was followed from the onset of infectious mononucleosis to the development of cirrhosis three years later This was verified by needle biopsy The etiologic relationship of the original infection to the cirrhosis cannot be positively determined since this man also consumed inordinate amounts of alcohol and did not maintain good nutrition Another case of cirrhosis following infectious mononucleosis has been reported in the foreign literature

Thus it can be concluded that while the hepatitis of infectious mononucleosis lasts only several weeks (two to four) a few cases may continue to show abnormalities for a prolonged period of time and occasionally cirrhosis may develop

Laboratory Findings

The number of patients who show clinical evidence of hepatitis (jaundice and hepatomegaly) are but a small fraction of those who show laboratory evidence of hepatic involvement Cohn and Lidman were the first to point out that nonjaundiced patients with infectious mononucleosis show abnormal liver function tests All of their 15 patients had a normal serum bilirubin but all showed abnormal thymol turbidity and bromsulphalein retention Seven of eight patients tested showed an elevated alkaline phosphatase In two other studies (Evans and Iversen and Raaschov) the patients had no hyperbilirubinemia but showed abnormal flocculation tests elevated alkaline phosphatase and BSP retention

The Table 45 from Jordan and Albright summarizes the laboratory findings in 301 patients with infectious mononucleosis Contrary to the title of the table a few of these patients were clinically jaundiced and 25% showed elevated serum bilirubin The noteworthy thing is that nearly all of these had one or more abnormal liver function tests 81% had positive cephalin cholesterol flocculation while over 60% had abnormal thymol turbidity alkaline phosphatase and bromsulphalein retention In the series reported by Bennett and co workers the thymol turbidity was elevated in 81% and the cephalin cholesterol in 79%

Abnormal serum protein partition has also been noted in the hepatitis of infectious mononucleosis Evans found depression of albumin and elevation of the gamma globulin in two patients by electrophoretic analysis Likewise I found gamma globulin elevation in 7 of 10 patients convalescing from infectious mono

36 — Infectious Mononucleosis

INFECTIOUS mononucleosis is an acute febrile disease of obscure causation but probably viral, characterized by abnormal lymphocytes in peripheral blood and tissues and high agglutination titer for sheep erythrocytes It is also frequently called glandular fever

Pathology

Pathologic proof of the frequency and nature of liver involvement stems from postmortem and biopsy material The former is not abundant because these patients seldom die Ruptured spleen and accidental death have furnished most of the autopsy material

The lesions consist of focal periportal and intralobular infiltration with lymphocytes and mononuclear cells of reticuloendothelial[1] origin Necrosis of liver cells is occasionally observed This was observed in only one of nine fatal cases reported by Cusher and Smith who concluded that these changes are difficult to distinguish from those in mild epidemic hepatitis It is not worthy that no patient with infectious mononucleosis died from acute yellow atrophy

Bang and Wanscher studied four icteric patients with infectious mononucleosis by needle biopsy They found the parenchymatous changes less marked and the interstitial changes more marked than in epidemic hepatitis No parenchymal necrosis was noted but mild degenerative changes such as vacuolization and granularity of cytoplasm No increase of fat or fibrosis was noted Portal areas were found infiltrated with lymphocytes plasma cells neutrophils and eosinophils The Kupffer cells were swollen and showed occasional mitosis Biliary thrombi were seen in the bile capillaries but not in the larger bile ducts indicative of intrahepatic obstruction The biopsy observations of Wadsworth and Keil are essentially in agreement with the above

Pathology—Summary

Focal infiltration with lymphocytes and other mononuclear cells periportal and intralobular

Necrosis of liver cells—rare

Changes simulate mild, infectious hepatitis parenchymatous changes less marked and interstitial exudative changes less marked

Kupffer cells—swollen, and occasional mitosis

Bile capillaries—show bile thrombi

Clinical Features

The clinical evidence of hepatic involvement consists of jaundice hepatic enlargement and tenderness Some of the asthenia anorexia and other gastrointestinal symptoms may be attributable to the hepatitis

Icterus is not a common clinical finding it is seen in 5 to 10% of cases In Kruger and co workers series of 63 patients only one was jaundiced (1 5%) while in the series from Hines Hospital 11% were jaundiced Slightly elevated serum bilirubin that is mild subclinical jaundice is more common as will be seen later It was originally thought that the jaundice in this disease is post hepatic because of pressure of enlarged lymph nodes on the common duct The histologic studies and the laboratory observations to be discussed all point to the hepatogenous origin of jaundice The jaundice usually develops in the first week of illness but may develop at the end of the second week when the patient is convalescing The duration of this symptom is 7 to 5 days In isolated instances the jaundice has lasted much longer—6 weeks (Wechsler) and 11 weeks (Abrams)

Hepatomegaly varies a great deal in its incidence in different series of cases tenderness is not specifically mentioned by some and is included with liver enlargement by others The interesting point about the hepatomegaly is that it is far less common than splenomegaly in this disease Thus Contratto found no hepatic enlargement or tenderness in any of his 196 cases of infectious mononucleosis but splenomegaly was noted in 91 (46%) Pre-

- Nausea
- Anorexia

Chronic Hepatitis—Cirrhosis (?)

- Abnormal liver function tests may continue for many months
- Cirrhosis and permanent liver injury are extremely rare; cases of cirrhosis following infectious hepatitis have been reported

Laboratory Findings—Summary

Liver function tests are abnormal even in the anicteric patients

- Cephalin cholesterol flocculation positive
- Thymol turbidity positive in 60–80% of patients
- Serum protein: elevated globulin, occasionally depressed albumin
- Alkaline phosphatase elevated
- BSP retention
- Urine—urobilinogen and coproporphyrin are increased

Diagnosis

The diagnosis of infectious mononucleosis on first examination of the patient is not easy. This is demonstrated by the series reported by Stevens et al in which a correct diagnosis was made in only 7.1% on admission. Other diagnoses included were acute follicular tonsillitis, acute pharyngitis, influenza, leukemia, cervical adenopathy, infectious hepatitis (3.3%), diphtheria, pyelonephritis, Hodgkin's disease, rheumatic fever, and chronic nervous exhaustion.

Our chief interest here is in differentiating this disease from infectious and homologous serum hepatitis. The differential features generally emphasized are those in the realm of the laboratory, but the clinical difference is no less important.

Fever is an almost constant feature of infectious mononucleosis and is frequently as high as 104 F and even 106 F has been reported. Chills may precede the rise in temperature. Fever is almost never present in homologous serum hepatitis and is low grade in infectious hepatitis. *Adenopathy*, especially cervical and frequently generalized, is almost universally found in infectious mononucleosis and is rare or absent in viral hepatitis. *Hepatomegaly* and *splenomegaly* are reversed in their frequency in the two diseases. While splenomegaly is observed in about 50% (or more) of patients with infectious mononucleosis, the liver is usually reported as enlarged in half that many. In viral hepatitis the liver is almost always enlarged but the spleen may be palpably enlarged in only 20% of cases. Clinical icterus is an uncommon feature in the hepatitis of infectious mononucleosis but is very common in viral hepatitis. These clinical points of differentiation (Table 46) may not always be conclusive and the corroboration of the laboratory may be needed.

The *laboratory* tests considered diagnostic of infectious mononucleosis are the differential leucocyte count and heterophil antibody agglutination. An increase of mononuclear cells and or the presence of an atypical lymphocyte (Downey cell) are considered diagnostic features. In the Mayo Clinic series 97% of the 210 patients showed positive findings in the blood smears. The heterophil antibody ag

Table 46

Differential Diagnosis between Infectious Mononucleosis and Viral Hepatitis

Symptoms and Findings	*Infectious Mononucleosis*	*Viral Hepatitis*
Fever	Almost invariably present. High up to 104 to 106	Rare or low grade
Chills	May occur	Do not occur
Adenopathy	Very common. Generalized—marked	Uncommon; if present not marked
Hepatomegaly	About 25% of cases	In almost all cases
Liver tenderness	Mild and not always	Marked and almost always
Splenomegaly	50% or more	10–20% of cases
Icterus	10% of cases	80% of cases
	Laboratory Tests	
Differential count	Increased mononuclear cells. Atypical lymphocytes	Usually normal or slight lymphocytosis
Heterophil antibody titration	Positive in high titers	Negative or occasionally weakly positive

TABLE 45

Liver Function Tests in 301 Cases of Infectious Mononucleosis Without Jaundice as Reported by Various Authors

Author	Number of Cases	Icteric Index or Blood Bilirubin			Urine Urobilinogen			Cephalin-Cholesterol Flocculation			Thymol Turbidity			Alkaline Phosphatase			BSP Retention			Comment
		No*	†	%	No	†	%	No	†	%	No	†	%	No	†	%	No	†	%	
Cohn & Lidman	15	15	0	0	0			0			15	15	100	8	7	88	15	15	100	Impairment indicated ll cases by two o more tests
Carter & MacLagan	18	0			0			0			18	10	56	0			0			Also f nd bno al al es in rh ru heumatoid arthr tis heart f il re & e docard tis
Gall	33	19	8	4	0			25	3	9	14	13	93	33	9	85	0			So e d gree of ter f re ce w th function in 31 of 33 pts
DeMarsh & Alt	19	19	5	6	0			18	15	83	0			0			19	15	9	Some e idence of fun t nal i pair ent in ll cases
E ns	19	19	0	0	0			19	1	89	19	13	68	11	6	43	1	1	100	E idence of bnor al ty in 18 of 19 cases egat re e lts n c trols
Peterson	39	39	15	38	39	21	54	39	26	6	30	18	46	11	8	3	32	19	59	E d ce of impa r m t in 20 of 39 cases by 3 o more te ts
Brown Sim White & Clifford	83§	4	8	38	68	3	34	8	0	85	77	38	49	0			41	0	49	Res lts f 1 more tests abnormal in 3 of 83 cases
F t & Dott	9	0			0			0			9	8	89	0			0			Also found abnormal v l es virus i e ons seo ndary pl m la s kle cell ne
I so & Raasch	24	33	0	0	33	0	0	0			33	24	73	0			0			Thy l t b d ty lso creased in 71% f cases of measles
A gl	20	11	4	36	0			10	13	68	0			0			17	13	6	E l ce of f nc t nal impairment in 18 of 20 cases
Jordan & Albright		20	2	10	14		50		17	7	2	18	8	^0	7	35	17	1	1	So bnormality in 1 of 2? cases im pa m t by 3 or ore tests in 15 of ?? cases
Total	301	249	6	25	154	51	33	4	191	81	246	15	64	86	56	65	14.	95	67	

W S Jordan and R W Albright Liver Function Tests in Infectious Mononucleosis J of Lab & Cl Med 35 688 1950

* Number of cases in which test was done

† Number of cases with abnormal values

‡ From tho s tabulated table

§ No st tem t gard g cl nical j nd

nucleosis using the chemical technique of Wolfson and Cohn

Increased urinary excretion of urobilinogen and coproporphyrin is further laboratory evidence of hepatic dysfunction

Clinical Features—Summary

Acute Hepatitis

Icterus—5–10% of cases

Usually begins in 1st week occasionally in 2nd week

Duration—7–25 days (extreme 11 weeks)

Due to intrahepatic changes

Hepatomegaly—15–27% of cases

Hepatic tenderness

Splenomegaly

Twice as frequent as hepatomegaly

It is characterized clinically by a short incubation period (10–40 days) general malaise low grade fever abdominal symptoms enlargement and tenderness of the liver and jaundice pathologically by centrilobular necrosis and a periportal exudative process

Homologous serum hepatitis is clinically and pathologically indistinguishable from infectious hepatitis but its incubation period is 45 to 160 days and it is transmitted by parenteral administration of human blood or blood products

BACKGROUND

Hepatitis came to the fore in World War II first because of the outbreak of jaundice following yellow fever vaccination (1942) and later because of the occurrence of many cases of the epidemic form in the African theater and the South Pacific It is not as has been assumed injudiciously by some a new entity but has been occurring off and on for many years most conspicuously in time of war and among military establishments It has been referred to as jaundice of campaigns jaundice of camps and military jaundice

During the three years of the American Civil War 52 133 cases occurred among Federal troops alone During the Franco-Prussian War 2 344 cases were observed in the Prussian Army and in the South African War there were 5 648 cases In World War I the disease occurred among British French Rumanian and German troops

ETIOLOGY

Medical attention became focused on acute hepatitis by the occurrence of over 6 000 cases of hepatitis after the use of yellow fever vaccine in the American Army during World War II It therefore seems reasonable to discuss the etiologic relations of this form of the disease first

Outbreaks of jaundice after yellow fever vaccination were reported by Brazilian observers in 1939 There were four possibilities regarding the exact nature and source of the icterogenic effect

1 Poor attenuation of the yellow fever virus
2 Contamination of seed virus
3 Agent unrelated to vaccine
4 Icterogenic action of human serum

The first three possibilities were excluded by epidemiological and pathological considerations

That human serum may be the source of an icterogenic agent was pointed out in 1885 by Lurman after the use of human lymph in vaccination Jaundice was reported following the use of measles immune serum by McNalty (1938) Propert (1938) Johnson and Jarvis (1940) and the Ministry of Health 1943) McNalty reported an especially virulent epidemic Of 100 children vaccinated 37 developed jaundice and 7 died The occurrence of jaundice following the use of mumps immune serum was reported by Gordon in 1942 and by the Ministry of Health in 1943 Transfusions of whole blood have been held responsible for the development of jaundice by Beeson (1943) Morgan and Williamson (1943) and the Ministry of Health (1943) In 1945 Grossman Stewart and Stokes and Rappaport reported a preponderance of jaundice among wounded military personnel who received blood and or plasma infusions within four months before onset of disease Evidence has also accumulated that the occurrence of hepatitis in syphilis clinics in which patients are undergoing treatment with arsenicals is due to transmission of minute amounts of serum from one or more patients who apparently carry the icterogenic agent in their blood stream It appears that the disease was transmitted in a similar manner in some diabetes clinic

In 1940 Sergiev made the following crucial observation Of 750 cases vaccinated against sandfly fever 9 subsequently developed jaundice The serum used in the preparation of this vaccine was injected into four other persons and jaundice developed in all while 14 persons injected with serum from different donors remained free of jaundice In this instance the relation of the human serum used in the vaccine to the icterogenic agent was well established

Evidence that the human serum was the vehicle for the icterogenic agent in yellow fever vaccine is abundant Only certain lots of

glutination test is positive in 80–90% of cases and the titers may be very high (1 7168) The positive reaction may occur late in the disease and even during convalescence therefore serial tests should be done While some abnormal lymphocytes and occasional lymphocytosis have been observed in viral hepatitis this is neither common nor marked The same may be said of the heterophil agglutination titer Havens and co workers found only 3% of 508 soldiers with viral hepatitis showed a titer of 1 56 and this was reduced to 1 7 or negative by absorption technique This technique (Davidson) should be used in doubtful cases

The clinical and laboratory features should suffice to differentiate these forms of hepatitis Berk and co workers also called attention to the lesser frequency of cholesterol ester depression and bromsulphalein retention in infectious mononucleosis The latter is contradicted by other workers An alkaline phosphatase elevation in the absence of jaundice is thought by them to be more frequent in infectious mononucleosis than in viral hepatitis

Treatment and Prognosis

Since hepatitis is so frequent an accompaniment of infectious mononucleosis the treatment of the acute disease should proceed with this in mind In other words absolute bed rest and a nutritious high protein diet are imperative The reported patient with cirrhosis following infectious mononucleosis received only two days of bed rest during the initial illness

In spite of the many similarities between the hepatitis of this disease and 'viral hepatitis the conclusion is inescapable that the prognosis sequelae and complications of the former are infinitely milder Death from diffuse hepatic necrosis has not been reported and while the disease may contribute to the development of cirrhosis in an occasional case the danger is not very great

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Infectious and Homologous Serum Hepatitis Etiology and Pathology

The oldest term applied to this clinical entity is catarrhal jaundice which was used by Bamberger in 1855 and by Virchow in 1865 Acute infective hepatitis has been referred to also as acute infectious hepatitis epidemic hepatitis infective jaundice infectious jaundice and epidemic jaundice Erroneously it has been called acute cholangitis The term infectious hepatitis for the naturally occurring disease has gained wide usage in the United States In the British literature infective hepatitis is most commonly used This has an advantage over the American terminology inasmuch as Weil s disease has been referred to as 'infectious jaundice or hepatitis

The form of this disease transmitted by human blood products has been referred to as homologous serum hepatitis or homologous serum jaundice and under certain circumstances as post vaccinal jaundice or hepatitis The all inclusive term viral hepatitis has been used for the entire group

Acute infectious hepatitis is an acute infectious mildly contagious disease occurring epidemically or sporadically caused by a filtrable virus which is transmitted to succeeding hosts by the pharyngeal or alimentary route

1 The clinical features are identical or so similar as to be undistinguishable It has been said that fever is more likely to occur in the early stage of infectious hepatitis but fever has been reported in as high as 51 per cent in some studies of post vaccinal hepatitis (Fox Mauso Penna and Para 194)

The morphologic changes are identical

3 Infective hepatitis has been transmitted by inoculation of serum from patients with the disease to normal volunteers proving that the naturally-occurring disease can be transmitted in the same manner as the homologous serum hepatitis (Newman 194 Cameron 1943 MacCallum and Bradley 1944 Murphy 1945)

4 While homologous serum hepatitis is not commonly spread by contact such transmission is not unknown The explanation for its rarity is twofold (a) many persons especially in older age groups are immune to the disease and (b) the unusual mode of invasion of the virus (parenteral) may attenuate it and make it less likely to spread But contact transmission of serum hepatitis by children who acquired the disease after immunization with convalescent measles serum was reported by Propert (1938)

5 Homologous serum hepatitis has been transmitted by

- (a) serum administration
  - (1) subcutaneously
  - (2) intramuscularly
  - (3) intravenously and
  - (4) pharyngeally by spray
- (b) pharyngeal secretions

Since pharyngeal transmission is thought by some to be the natural route for epidemic hepatitis the two diseases can be transmitted in a similar manner However infective hepatitis is transmitted by fecal matter and this mode of transmission has not been observed for homologous serum hepatitis

6 The variation in the incubation period of the two diseases may be due to the difference in mode of transmission rather than to a difference in the virus It has been shown in human transmission experiment that the incubation period varies with the source and method of introduction of the infective material Thus serum introduced subcutaneously produced the disease in normal volunteers after an incubation period of 64 to 92 days while saline washings of feces and nasopharyngeal secretions sprayed into the nasopharynx produced the disease in 4 to 31 days (MacCallum and Bradley 1944 Findlay and Martin 1943) This observation is contradicted by the observation that IH virus may be transmitted by syringe and blood products and give a shorter incubation period (Henle et al 1950) The fact that other viral infections may produce hepatitis complicate the diagnostic and epidemiologic problem Hepatitis caused by what appeared to be the virus of herpes simplex has been reported (Zuelzer and Stulberg)

Epidemiology of Viral Hepatitis

Etiologic and epidemiologic study of hepatitis is handicapped by the impossibility of transmitting the active agent to laboratory animals One report that the disease is transmissible to or is found in animals came from a Scandinavian investigator Andersen (1937) who pointed out that epidemic hepatitis is more common in rural areas than in the city and that pigs develop an epidemic form of jaundice He postulated that the disease can be transmitted from the pig to man and produced the disease in these animals by feeding them livers from diseased animals He also produced the disease in pigs by feeding them 50 cc of duodenal contents from human beings with jaundice Only undernourished pigs however were susceptible to its transmission in this manner

Another suggestion that transmission to animals may be possible under certain circumstances comes from MacCallum and Miles (1946) The investigators were able to produce hepatic necrosis in rats on a deficient diet following inoculation of tissue from other animals who were exposed to blood nasal washings and excreta of patients suffering from hepatitis The nature of the experiments do not offer conclusive proof that an icterogenic virus was responsible for the hepatic necrosis

Mode of Transmission

Direct contact and hence droplet infection through the nasopharyngeal and respiratory

yellow fever vaccine were icterogenic The only difference in these lots was in the serum used in their preparation Several of the icterogenic lots were made from serum from the same donors Some of the donors were contacted and gave a history of jaundice at variable periods before they were bled

Transmission experiments with human volunteers offer direct proof that the serum is *the vehicle for the icterogenic agent* Serum obtained from patients in the early icteric stage of post vaccinal hepatitis produced jaundice in normal persons (Oliphant Gilliam and Larson) Serum obtained from patients with epidemic hepatitis also transmitted the disease to normal persons after subcutaneous injection (Cameron) showing that the virus circulates in the blood stream in the naturally occurring disease as well

MacCallum and Bauer studied the vaccine which produced jaundice in 30 to 40 per cent of vaccinated persons When the pooled serum used in this vaccine was injected into normal volunteers the rate of jaundice equaled that following vaccination All this evidence substantiates the idea that human serum is the source of the icterogenic agent When human serum was abandoned in the preparation of yellow fever vaccine the incidence of jaundice following its use returned to the control level

This impressive array of evidence as well as the accumulated clinical experience in the last few years proves that so called normal human blood plasma and serum may harbor an agent or agents capable of producing hepatitis when administered parenterally

What if any is the etiologic relation between homologous serum hepatitis and infectious hepatitis?

The evidence which tends to refute the *identity of these two diseases is as follows*

1 The incubation period is usually less than a month in infectious hepatitis but as long as 160 days or more in the homologous serum hepatitis Since we ordinarily think of each micro organism or virus as having a constant incubation period this difference has been used as an argument against the identity of the two diseases

2 The mode of transmission is by definition different The homologous serum hepatitis virus (SH) is transmitted solely through parenteral administration of human blood products while the spontaneously occurring disease (IH virus) is transmitted from host to host by direct contact or through ingestion of excreta There is evidence now that infectious hepatitis (IH) virus can be transmitted by inoculation with serum from a person harboring this virus (Paul and Gardner 1950 Neefe 1949) This may explain the very short incubation period occasionally seen in hepatitis acquired by inoculation

3 It has been said that there is no epidemic spread of serum hepatitis and therefore it cannot be the same disease as infectious hepatitis which unquestionably occurs in epidemics

4 These two diseases appear to differ immunologically Beattie and Marshall (1944) observed that the American troops exposed to homologous serum hepatitis because of inoculation with yellow fever virus were immune to homologous serum hepatitis but readily developed infectious hepatitis while British troops in the same hospital were susceptible to homologous serum hepatitis and immune to infectious hepatitis

Neefe Stokes and Gellis carried out transmission experiments on human volunteers with material obtained from patients with serum hepatitis and infectious hepatitis They noted that the inoculated individuals developed immunity to one form of the disease but not to the other This suggests that the two conditions are immunologically different and due to different agents However even the persons re inoculated with the homologous serum virus showed some changes in liver function but not a frank hepatitis

5 A skin test has been described (Henle et al 1950) which gives a uniformly positive response in patients who have had infectious hepatitis while individuals with a history of serum hepatitis show a positive response in only 40% similar to individuals without history of hepatitis This also suggests that virus IH and SH are antigenetically different

The evidence which favors the proposition that the two diseases are identical is nevertheless imposing

occurs after a blood transfusion or plasma infusion several hundred cubic centimeters of virus containing material are administered and yet the disease is no more severe or likely to be fatal than when a fraction of a cubic centimeter of serum is administered in yellow fever vaccine inoculation The explanation of this phenomenon is not simple It is likely hat the antibodies in roduced in the larger amount of plasma tend to neutralize the larger amount of virus Another possible explanation is that in the process of storage and preparation of the yellow fever vaccine the virus originally introduced actually multiplies and the efore equals in potency that obtained in a blood transfusion The virus has been cultured on chick embryo medium passed through several generations and still was able to produce the disease The final dilution calculated from the or ginal serum used was 1 10 000 000

Etiology—Summary

Homologous Serum Hepatitis (SH)
  Agent transmitted by inoculation
    1 Blood or blood products
    2 Any inoculation with needle
      a parenteral therapy
      b tatooing
      c drug addicts
Infectious Hepatitis (IH)
  Agent gains entrance
    1 By oral route through ingestion of food
      a contaminated by feces
      b contaminated by urine
    2 By respiratory tract droplet infection
Evidence that SH and IH Viruses are not Identical
  1 Incubation period differs
  2 Mode of transmission different
  3 Serum hepatitis does not occur in epidemic form
  4 No cross immunity
  5 Skin test does not give identical reaction in two diseases
Evidence that SH and IH Virus may be Identical
  1 Clinical features are nearly identical
  2 Pathological features are identical
  3 IH virus can be transmitted by inoculation
  4 SH virus may be transmitted by contact
  5 SH virus has been transmitted by serum and pharyngeal secretion applied to pharynx
Nature of Virus
  1 Cannot be inoculated into laboratory animals
  2 Passes through Berkefeld filter
  3 Resists heating to 56 C for 30 to 60 minutes
  4 Res sts drying in vacuo
  5 Survives storage at 40° F
  6 Destroyed by ultraviolet light
  7 Destroyed or attenuated by storage at 80 F
  8 As little as 0 001 cc of infected serum can produce disease

PATHOLOGY

Liver

Gross In 1 5 cases of fatal hepatitis Lucke reported that the liver was the site of the principle lesions and the changes in the liver were indistinguishable from those ascribed to idiopathic red or yellow atrophy

The liver is usually reduced at times to less than half of its normal size Frequently this organ weighs 800 to 1 00 gm However this is variable The weight of the liver varies between 600 and 400 gm and in one fifth of the cases the liver is normal in size In general the smaller livers occur in patients who die within the first five weeks of illness In the more chronic disease hyperplasia compensates for the loss of parenchyma

The surface is smooth or finely granular in the early stages Later it is coarse and nodular or shows large tumor like masses termed diffuse nodular hyperplasia This variation depends on the degree of parenchymal compensatory hyperplasia Shrunken areas intervene among the areas of hyperplasia and are the seat of parenchymal necrosis (Fig 42)

The consistency of the organ varies according to the stage of the disease In the early stages the liver is flaccid and flabby Later the collapsed parts become tough The nodular areas have the same consistency as normal liver

The color of the various portions of the liver varies The nodules are ivory colo or yellowish green depending on the degree of bile retained in them The shrunken areas are dull red or grayish

tract seemed at first the most likely mode of transmission This was suggested by the frequency of rhinitis pharyngitis and upper respiratory symptoms early in infectious hepatitis These symptoms are usually absent in homologous serum hepatitis Moreover the nasopharyngeal washings obtained from patients with infectious hepatitis can produce the disease in volunteers by pharyngeal introduction

The seasonal fluctuations of the disease with the highest prevalence in autumn and early winter (Paul and Gardner 1950) is in keeping with the spread of respiratory diseases

The intestinal-oral circuit is probably the commonest route of spreading the disease from one individual to another Several investigators succeeded in producing the disease in human volunteers by administering Berkefeld filtered extracts of infected feces in liquid form by gastric tube or in gelatine capsules The commonest symptoms in patients suffering from infectious hepatitis are gastrointestinal Almost 20% of patients suffer from diarrhea In military establishments the incidence was highest where proper disposal of excreta was impaired With the establishment of better control of water supply and disposal of excreta the disease was drastically curtailed The disease is also most common in newly arrived personnel in the younger age groups In those 20 years of age the disease is twice as common as in those 40 years of age (Paul and Gardner 1950) The disease is common in infants and children It occurs in epidemic form among children living in institutions such as orphanages (Bennett et al 1952)

The agent is also thought to be excreted in the urine Neefe and Stokes (1945) pointed out that the agent can be transmitted by the contamination of the water supply carrying the agent from the excreta to the food supply Water borne and food borne epidemics of hepatitis have been reported (Farquhar et al 1952 Kaufman et al 1952) I have seen infectious hepatitis transmitted to nurses who cared for psychotic children with hepatitis The source of the infectious agent was most likely the feces which the children disseminated throughout their immediate environment Ordinary means of water purification are ineffective but boiling for five minutes destroys the virus (Neefe 1949)

SH virus is known to be transmitted by blood or blood products by needles and syringes contaminated by serum and possibly by tatooing (Smith 1950)

The duration of the infective stage and the length of time that viable virus remains in the body of the individual convalescing from hepatitis is of utmost clinical importance While it is thought that infectivity decreases after icterus appears the potent virus may remain in the body for an indefinite period of time Contributors to icterogenic pools of serum gave a history of having had jaundice 20 years before The passage of viable virus in the stools for 5 to 15 months has been demonstrated by the use of human volunteers (Capps and Stokes 1952, Bennett et al 1952) In the present state of our knowledge it must be assumed that the carrier state may occasionally persist the entire life span of the individual

Nature of the Icterogenic Agent

The icterogenic agent has never been successfully inoculated into laboratory animals It passes through a Berkefeld filter and withstands heating at 56 C for 30 to 60 minutes It also withstands drying in vacuo as well as storage at 40 F It is able to produce the disease after prolonged and variable incubation periods All these properties except the first one are common to viruses and constitute evidence that the agent is a virus The agent is destroyed by ultraviolet irradiation and perhaps destroyed or attenuated by storage at room temperature (80 F) for three to six months (Allen et al 1950) The virus can apparently be destroyed by methyl bisamine (beta chlorethyl) (Hartman et al 1949) The agent is extremely potent A single dose of yellow fever vaccine contains 0 04 cc of serum and if only one of the 40 possible donors contributed the icterogenic agent as little as 0 001 cc of his serum could be responsible for the disease There is no apparent relationship between the amount of virus administered and the severity of the disease When hepatitis

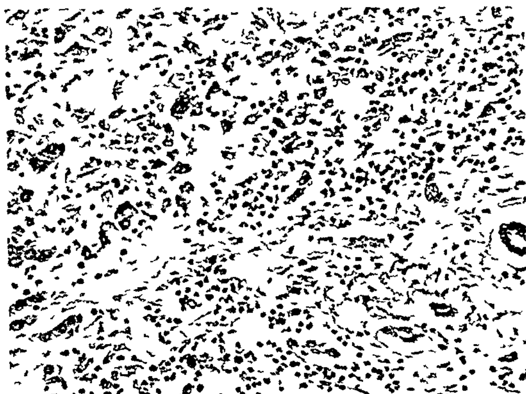


Fig 4 Micro opic sect n of li r (X oo) f m p tent with I tal hepatiti h wing ma n c h p t c p nch ma with o l t w c tt r d parenchymal ll r cog t abl nd i filtrati with m nucl a ll S r l b l d ct r n C s p tmen h w n Fg 4

Some of the information obtained from both sources coincides One point of major clinical significance is that in mild as well as in fatal disease there is evidence of involvement of the hepatic parenchyma that is the condition is a true hepatitis rather than *an involvement of the* bile passages or a catarrhal inflammation of the bile ducts Also the pathologic information obtained from these various sources reveals no structural difference between the homologous serum hepatitis and the epidemic form

It is important for the clinician to keep in mind that there are two processes going on in the liver of *every patient with hepatitis* and that the clinical features laboratory features diagnostic complexities and prognosis depend to a considerable degree on which of these two processes predominates These two processes are *necrosis* of liver cells and an *exudative process* *If the necrosis* predominates the patient is much sicker and there is much laboratory evidence of parenchymatous damage If the exudative process predominates the disease is milder and the jaundice may have most of the features of posthepatic jaundice since the d st rbance s chiefly in the outflow of b le

The exudative proc ss s *most marked peri*portally but is also intralobular the cells are predominantly mononuclear but polymorphonuclear cells and eosinophiles are also seen

When necrosis is minimal it is confined to the centrilobular area while normal cells *may be* present *in the periphery* The autolysis of the cells seems to be very rapid since no cell debris remains The necrosis becomes widespread in the severe form of the disease involving the entire lobule (Fig 43) The exudative process also increases with more widespread necrosis Some parenchymal cells consist of a homogeneous eosinophilic cytoplasm and others show hyaline inclusion bodies Granules of a yellow brown pigment (lipochrome) are found in the Kupffer as well as parenchymal cells (Mallory 194) Glycogen is abundant in surviving cells

In the recovery stage as seen by biopsy there is a regression of these changes The exudation is absorbed with a gradual disappearance of inflammatory cells The parenchyma shows regeneration and proliferation In the center of the lobules are growing liver cell cords with large eosinophilic multinucleated cells

While fatty metamorphosis is not a part of the histological alterations in viral hepatitis it has been

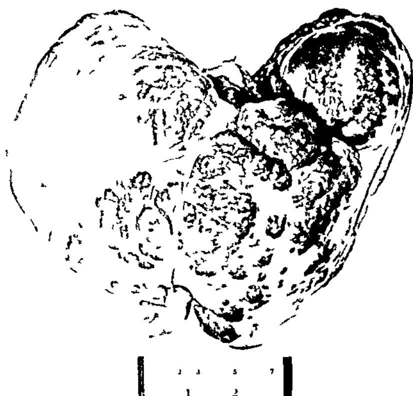


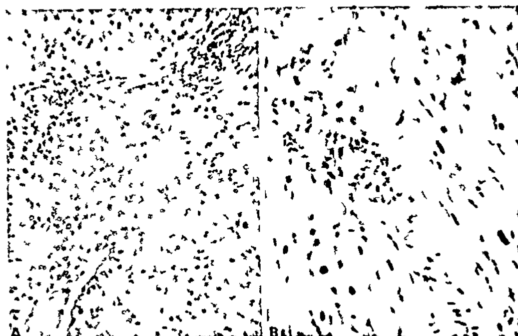
Fig 4 Homologous serum hepatitis This liver weighed 1840 grams This specimen is unusual since it shows marked atrophy with destruction of most of the parenchyma of the right lobe and tumor like hyperplastic nodes and enlargement of left lobe The right lobe was grayish yellow soft and flabby The nodules were reddish brown in color

This patient aged ... had a history of ulcerative colitis for 11 years Severe relapse 5 months previous with multiple blood transfusions The patient had jaundice 6 weeks before admission to the hospital Physical examination revealed marked weight loss icterus and pallor liver not palpable but tender on percussion ascites was evident Urine was positive for urobilinogen and bilirubin There was a trace of albumin Serum bilirubin 4 6 mgm% Total cholesterol 16 mg% Ester 91 mg% Prothrombin time 16 sec 41% of the normal Cephalin cholesterol flocculation 4 plus Thymol turbidity o units Alkaline phosphatase 14 6 Bodansky unit Total protein 8 0 Albumin 7 Globulin 5 3

yellow The color also varies with the stage of the disease and the vascularity of the organ If death occurs early the liver is hyperemic red and flabby hence the term acute red atrophy If death is postponed for several weeks the hyperbilirubinemia imparts a yellow color to the liver (acute yellow atrophy) In the later stages with more compensatory nodular hyperplasia the term subacute yellow atrophy has been applied Still later with increase in the hyperplastic nodules which are green and the contracted shrunken areas—yellow or red—a picture referred to as post necrotic cirrhosis develops

The cut surface shows even greater variability in appearance than the surface The red shrunken areas show obliterated or indistinct markings The pale yellow or green nodular areas show distinct lobulation The organ is not affected uniformly much loss of tissue is present in one area and hyperplasia in another In general the left lobe is shrunken and collapsed while the right lobe shows hyperplasia

Microscopic Our knowledge of the microscopic pathology of the disease is derived from biopsy as well as autopsy material The biopsy material gives a kaleidoscopic picture of the architecture of the liver in the various stages of the disease Thus we can follow the disease pathologically from its inception through the symptomatic stage to recovery and can study mild as well as severe disease In the autopsy material we have the advantage of studying the entire organ in detail and not a minute specimen obtained blindly however in this material we see only the final stage of the fatal disease



F g 44 A H pa t s and m ocard M c osc p c sect on f l ver (X 40) at a p show ng m ked d l on a d engorg m t f s d and m d zon l necros of l v r c lls and lymphoc t c fil rat on An unu al type f a hep r

B M crosc p c sec ion (X 200) of myoc d m showing f gment n of m cl fibres and l mphocyt c nfil (Cour e of Dr O o S ph r D partment of Pa h gy M cha l Reese H p l Ch g)

Pa w s m le 6 ye rs of ag n whom c culatory collapse and shock m rk d the en cl cal co rs

hemorrhages are found n the lungs The alveol and bronch are f equently foun l floo led w th blood result ng n bacter al nvas on and term nal pne mon a In the k dneys the hemorrhages are usually n the pelv c reg ons

The k dneys n add t on are frequently swollen flacc d and b le sta ned show ng cholem c nephros s m croscop cally The glomerul are normal n ap pearance but prec p tated prote n s frequently found n the capsular space The tubules show vary ng degrees of degenerat ve change

The changes n the bra n are of nterest for two reasons first the term nal symptoms in fatal d sease are almost always cerebral and second becaus of the quest on of a spec fic neu otrop c effect of the v rus Grossly the b a n shows pr nc pally edema The changes found m croscop cally are of two types ac te degenerat on of gangl on ce ls and nflammatory react on aroun l vessels and in the men nges The changes n general are non spec fic as n many ser ous and fatal d seases Iso-late l cells are completely destroyed and others show s gns of damage Gl al react on s sl ght In the basal men nges and around the vessels of the bra n ste n some per vascular lymphocyt c infiltrat on was fo n l Th s per vascular and men ngeal infiltra t on was seen n 15 per cent of Lucke s cases and was of suffic ent degree to be called a men ngoencephal t s

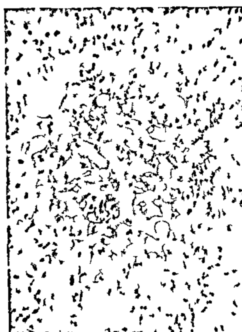
Wh le changes n the heart are usually nconsp cu ous and secondary to the hemo rhag c phenomenon Dr Otto Saph r recently demonstrated a case w th severe and w despread necros s of the myocard um (F g 44) The m d zonal necros s (F g 44a) seen n the l ver may cast some doubt on the ident ty of the et o og c v rus

Pathology—Summary

Liver

Gross

- **Size is reduced**
- **Surface smooth or finely granular early coarse and nodular later**
- **Consistency—flaccid and flabby early tough later**
- **Color varies according to stage loca tion and type of structural changes and absence or presence of jaundice —yellow red gray green**



! Fg 43a Needle bo; X 40 d mon s a ng a ty hang n j n w h b d ng h pa

descr bed and s prob h y a second r te tu e or perhaps precedes the development of hepat t s (F g 43a) Hemos der n accumulat n n the l er cells has also been l sc bed follo ng hepat t s (Hult 195)

The ret culum framewo k s gene ally p eserved The fibros s descr bed n tl e acute o sub cute stage of hepat t s may actually be condensat on of the ret culum However c rrhos s may n some n stances follo hepat t s (p 00) an l perhaps in those cases d srupt on of the ret culum frame ork precedes the fibros s

The s nuso ds are often great y engorged and the r endothe um s enlarged Occas onally they are collapsed Endophleb t s s seen n the hepat c ve ns espec ally the central lobular ve ns There may be thromb in the smaller ntrahepat c b le ducts One of the remarkable h stolog c changes is the tendency to prol ferat on of the sm ler or septal b le ducts In some are s where marked loss of l ver parenchyma has taken place many prol ferat ng and branch ng b le ducts can be seen Though the loss of l ver cells an l the collapse of the ret culum may g ve the appearance of duct prol ferat on by br ng ng many ducts together unm stakable ev dence of pro ferat on s p esent Whether these prol ferat ng b le ducts g ve r se to newly formed l ver cells s open to q est on From h stolog c ob servat on such an interpretat on may be made but many doubt that b le duct ep thel um can g ve r se to funct on ng l ver cells

The nodular areas are the seat of nodular hyper plas a as d st ngu shed from ntralobu ar regenera t on Morpholog cally and phys olog ca ly no m l lobules are not atta ned by th s type of egene a on Here and there solated l ver cords are se n sepa rated by collapsed stroma The s nuso ds are poor y formed and ischem c The ind v dual l e cells are larger and the cytoplasm is frequently smoo h and m lt nucleated Some l ver cells are not a ranged n cords at all but look l ke mult nucleated syncy a or are arranged n d sorderly groups sugge tive of neoplasms

L cke reported the appearance of the l ve n 1 pat ents who d ed of other causes 1 to 14 mon hs after they had recovered from nfect ous hepa t s In 9 cases the l ver sho ved complete anatom c res torat on In the other 3 m n mal changes we e s l v s ble suggest ng that complete restorat on was not yet accompl shed

Among the changes seen were the fol ow ng h lobular pattern as accentuated ow ng to rema n n nfiltrat on in the per portal stroma an occas onal cell was m ss ng n the central part of the lobu e and some mult nucleated cells were seen nd cat ons f recent hepat c cell prol ferat on were the large cel w th hyperchromat c nucle In some areas he b l ary d cts ere more consp c ous than norm l Sl ght prol ferat on of strands of stroma was seen here and there The wall of an occas onal e n show d th cken ng Nee lle b opsy stud es of con al s n hepat t s confirm these observat ons

Extrahepat c Pathology

The cond t on of the gallbladder and ex a hepat c b le luct s of nterest n v ew of the earl op n on of the pathogenes s of cata rhal jaund e In about one half of the cases stud ed the wa of the gallbladder was th ckened and showed some hemo rhages The extrahepat c b le ducts are a most al ways patent Occas onally nsp ssated mucus may form as a result of the general process

The duoden m s frequently nvol ed n an n flammatory process of the ent e ntest nal a A phlegmonous nflammat on nvol ng many port ons of the ntest nal tract and pa t cularly the leocecal reg on s a str k ng les on Non nflam matory edema of both the large and small ntest e is frequently found as well as ulcerat ons of the lower end of the esophagus

The spleen s found enlarged at autopsy m e frequently than cl n cally Some enla gemen s found n 75% of fatal cases In the ea ly s ages of the d sease the enlargement apparently s due to ce u a prol ferat on In the later stages enlarg ment s accompan ed by d lated s n so ds and s probably due to engorgement from portal hypertens on

Hemorrhages are w de y scattered the ntest nes and mesentery are the commonest s es next n order of frequency are the lungs heart k dney sk n and bra n Bra n hemorrhages are found n only c per cent of cases The hemorrhages vary n s ze from petech ae to large ecchymoses W desp ead and large

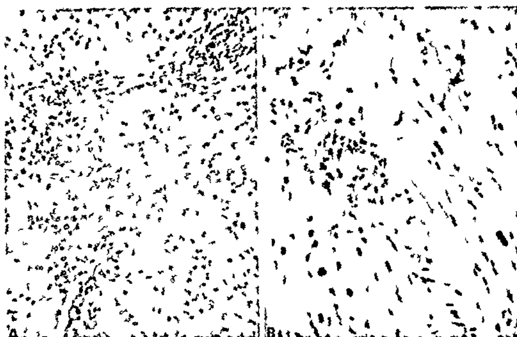


Fig 44 A H pat ti and m [illegible] d t Micro p c s cti n of l v r (X 140) at aut psy sho ing ma k d d l at t n a d ng rg me t of [illegible] nd m d [illegible] al necrosis (h [illegible] c ll and lymphoc tic infiltr t n An [illegible] u l esp [illegible] ral h pat t s

B Mic ograph [illegible] (X [illegible]00) of myoc rd um showing f gm nt ti n f m cl fibres and lymphocyt c nfilt t [illegible] (Co rt y of Dr Ott S ph r D pa tm nt of Path l gy M ch l R [illegible] H sp tal Chic go)

P t nt wa [illegible] m l 62 y [illegible] t g [illegible] n whom c rc l tory collapse nd sh ck mark d th [illegible] nt cl nical cou s

hemorrhages are found in the lungs The alveoli and bronchi are frequently found flooded with blood resulting in bacterial invasion and terminal pneumonia In the kidneys the hemorrhages are usually in the pelvic regions

The kidneys in addition are frequently swollen flaccid and bile stained showing cholemic nephrosis microscopically The glomeruli are normal in appearance but precipitated protein is frequently found in the capsular space The tubules show varying degrees of degenerative change

The changes in the brain are of interest for two reasons first the terminal symptoms in fatal disease are almost always cerebral and second because of the question of a specific neurotropic effect of the virus Grossly the brain shows principally edema The changes found microscopically are of two types acute degeneration of ganglion cells and inflammatory reaction around vessels and in the meninges The changes in general are nonspecific as in many serious and fatal diseases Isolated cells are completely destroyed and others show signs of damage Glial reaction is slight In the basal meninges and around the vessels of the brain stem some perivascular lymphocytic infiltration was found This perivascular and meningeal infiltration was seen in 15 per cent of Lucke s cases and was of sufficient degree to be called a meningoencephalitis

While changes in the heart are usually inconspicuous and secondary to the hemorrhagic phenomenon Dr Otto Saphir recently demonstrated a case with severe and widespread necrosis of the myocardium (Fig 44) The mid zonal necrosis (Fig 44A) seen in the liver may cast some doubt on the identity of the etiologic virus

Pathology—Summary

Liver

- Gross
  - Size is reduced
  - Surface smooth or finely granular early coarse and nodular later
  - Consistency—flaccid and flabby early tough later
  - Color varies according to stage location and type of structural changes and absence or presence of jaundice—yellow red gray green



Fig 43a Needle biopsy of a liver (× 140) demonstrating fatty change in a patient with subsiding hepatitis

described and is probably a secondary feature or perhaps precedes the development of hepatitis (Fig 43a) Hemosiderin accumulation in the liver cells has also been described following hepatitis (Hult 195)

The reticulum framework is generally preserved The fibrosis described in the acute or subacute stage of hepatitis may actually be condensation of the reticulum However cirrhosis may in some instances follow hepatitis (p oo) and perhaps in those cases disruption of the reticulum framework precedes the fibrosis

The sinusoids are often greatly engorged and their endothelium is enlarged Occasionally they are collapsed Endophlebitis is seen in the hepatic veins especially the central lobular veins There may be thrombi in the smaller intrahepatic bile ducts One of the remarkable histologic changes is the tendency to proliferation of the smaller or septal bile ducts In some areas where marked loss of liver parenchyma has taken place many proliferating and branching bile ducts can be seen Though the loss of liver cells and the collapse of the reticulum may give the appearance of duct proliferation by bringing many ducts together unmistakable evidence of proliferation is present Whether these proliferating bile ducts give rise to newly formed liver cells is open to question From histologic observation such an interpretation may be made but many doubt that bile duct epithelium can give rise to functioning liver cells

The nodular areas are the seat of nodular hyperplasia as distinguished from intralobular regeneration Morphologically and physiologically normal lobules are not attained by this type of regeneration Here and there isolated liver cords are seen separated by collapsed stroma The sinusoids are poorly formed and ischemic The individual liver cells are larger and the cytoplasm is frequently smooth and multinucleated Some liver cells are not arranged in cords at all but look like multinucleated syncytia or are arranged in disorderly groups suggestive of neoplasms

Lucke reported the appearance of the liver in 12 patients who died of other causes 1 to 14 months after they had recovered from infectious hepatitis In 9 cases the liver showed complete anatomic restoration In the other 3 minimal changes were still visible suggesting that complete restoration was not yet accomplished

Among the changes seen were the following the lobular pattern was accentuated owing to remaining infiltration in the periportal stroma an occasional cell was missing in the central part of the lobule and some multinucleated cells were seen indications of recent hepatic cell proliferation were the large cells with hyperchromatic nuclei In some areas the biliary ducts were more conspicuous than normal Slight proliferation of strands of stroma was seen here and there The wall of an occasional vein showed thickening Needle biopsy studies of convalescent hepatitis confirm these observations

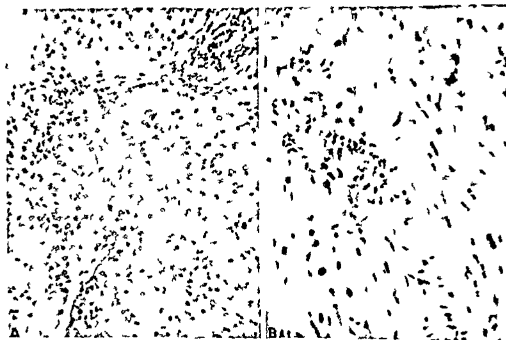
Extrahepatic Pathology

The condition of the gallbladder and extrahepatic bile duct is of interest in view of the early opinion of the pathogenesis of catarrhal jaundice In about one half of the cases studied the wall of the gallbladder was thickened and showed some hemorrhages The extrahepatic bile ducts are almost always patent Occasionally inspissated mucus may form as a result of the general process

The duodenum is frequently involved in an inflammatory process of the entire intestinal tract A phlegmonous inflammation involving many portions of the intestinal tract and particularly the ileocecal region is a striking lesion Noninflammatory edema of both the large and small intestine is frequently found as well as ulcerations of the lower end of the esophagus

The spleen is found enlarged at autopsy more frequently than clinically Some enlargement is found in 75% of fatal cases In the early stages of the disease the enlargement apparently is due to cellular proliferation In the later stages enlargement is accompanied by dilated sinusoids and is probably due to engorgement from portal hypertension

Hemorrhages are widely scattered the intestines and mesentery are the commonest sites next in order of frequency are the lungs heart kidney skin and brain Brain hemorrhages are found in only 5 per cent of cases The hemorrhages vary in size from petechiae to large ecchymoses Widespread and large



I g 44 A Hep s and m oc rd t s M cr scop c se t on of l ver (X 140) at a ps show g ... t on nd g rgement ts n d and m d zon l necr s of l ver c ll a d l mphocytic ... ual yp f al hepa

B M o cop c ec on X oo) of my c rd um show ng fr gm n a n of m scle fibres ... fi t n (Co o Dr O S ph D p m nt of Pa holog) M ch l Re se H p a C

P n w a mal b y a of age n whom c c l t ry c llapse and shock ma k d th er

hemorrhages are found n the lungs The alveol and bronch are frequently found flooded w th blood result ng n bacter al nvas on and term nal pneu mon a In the k dneys the hem rrhages are usually n the pelv c reg ons

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t on was seen n 15 per cent ... of suffic ent degree to be ca ... t s

Wh le chang s n the hea ... ous and secondary to the ... Dr Otto Saph r recently d... severe and w desprea l ... (F g 44) The m d zonal ... n the l ver may cas ... the et olog c v rus

Pathology—Summary

Liver

Gross

Size is reduced

Surface smooth or f ... ly granular early coarse and nodular later

Consistency flaccid and flabby early tough later

Color varies accord ng to stage loca tion and type of structural changes and absence or presence of jaundice —yellow red gray green

Microscopic
1 Necrosis
a *centrolobular or*
b *diffuse*
c rapid death of cells
2 Exudative process
a chiefly periportal
b also intralobular
c cells are predominantly mononuclear
3 Parenchymal cells may show
a hyaline inclusion bodies
b homogenous eosinophilic cytoplasm
c *glycogen in abundance*
4 Reticulum framework
a usually intact
b may be condensed
c may be disrupted in cases leading to cirrhosis
5 Vascular channels
a *sinusoids* are engorged
b endothelium and Kupffer cells are swollen
c endophlebitis
6 Bile ducts
a *thrombi*
b *proliferation*
7 Pigments
a lipochrome pigment in Kupffer and parenchymal cells
b hemosiderin accumulation
8 Fatty changes are uncommon

Extrahepatic
Gallbladder wall thickened and hemorrhagic
Extrahepatic bile ducts patent
Intestines may be involved in phlegmonous process, show hemorrhages
Spleen enlarged in 75% of cases
Kidneys *may show cholemic nephrosis*
Heart hemorrhagic subendocardial or myocardial

38—Infectious and Homologous Serum Hepatitis Clinical Features, Prognosis and Sequelae

Symptomatology

THE symptoms and findings of the epidemic or infectious form and the homologous serum variety of hepatitis are so nearly alike that the diseases are practically indistinguishable on this basis Some slight differences exist which will be pointed out when these symptoms and findings are discussed

The difference in the incubation period has already been mentioned but it should be reiterated that the virus of infectious hepatitis (IH) may be transmitted with blood or its products and in this case the incubation period may be short

The symptoms of the disease may be divided into three stages the first may be termed the prodromal the pre icteric or initial stage the second the icteric or intermediate stage and the third the convalescent or the fatal or terminal stage

Prodromal stage In the first stage the symptoms may be vague and mild and a diagnosis may be impossible When the disease is common a guess may be hazarded The patient complains of general malaise fatigue

aching sensations in various parts of the body or upper part of the abdomen Muscular and joint pains may suggest arthritis or rheumatism Anorexia may develop early nausea may also be present and less commonly vomiting Symptoms suggestive of an upper respiratory infection may usher in the disease This type of onset is more common in infectious hepatitis When complaints referable to the gastrointestinal tract predominate an erroneous diagnosis of gastroenteritis may be made especially when diarrhea is present But constipation is just as frequent or more frequent than diarrhea This stage lasts between five and ten days—usually about seven

Icteric stage The icteric stage may be ushered in by chilliness or a chill and fever This manifestation is more common in the epidemic form However Brazilian investigators of the early post vaccinal hepatitis reported fever in 51 per cent of these patients Before the jaundice appear the patient may notice the deep brown color of the urine and the decreasing color of the stools When the icterus first appears the other symptoms may increase especially those referable to the gastrointestinal tract The anorexia may become absolute with nausea and vomiting and ingestion of food may be suspended for a while However with the deepening icterus the symptoms begin to subside and in spite of the deep staining of the skin and conjunctivae the patient may develop a sense of well being This is the rule in the mild form of the disease The lack of correlation between the various symptoms and the degree of icterus is remarkable in some cases

Pain is a variable symptom being absent in some cases mild in others and occasionally of a severity requiring narcotics for relief It is usually constant and aching and may be boring or have a cramp like component suggesting cholecystitis The pain may simulate biliary colic This type of pain has been observed in malignant hepatitis in Sweden (Salvesen and Lodoen 1950) The pain may be in the epigastrium but more commonly occurs in the right upper quadrant radiating posteriorly Occasionally pain in the right lower quadrant suggest acute appendicitis The pain is frequently aggravated by jarring jolting deep inspiration or cough Pruritus is uncommon and may be absent in spite of deep icterus

In this stage of the disease one cannot always predict whether the patient will recover develop chronic liver disease or die

The icteric stage may be absent completely since anicteric hepatitis is not uncommon Its exact frequency is difficult to determine since icteric patients are often undiagnosed It is estimated that 20% of adults and the vast majority (90%) of children run the entire course without clinical icterus Especially in the younger age group the disease may be completely asymptomatic

Convalescent stage In the recovery stage all subjective symptoms disappear rapidly gastrointestinal complaints subside and the patient may develop a ravenous appetite and regain his lost weight The icterus after reaching a peak begins to subside at first rapidly but as a rule the rate levels off and a subicteric tinge to the conjunctivae may persist for some time (Case 5 p 27)

An attempt may be made to predict the course or the outcome of the disease by the severity of the early symptoms and the depth of the icterus However neither of these is an entirely reliable criterion

Persistence and increase in severity of gastrointestinal symptoms especially nausea and vomiting may forebode a fatal termination or an extremely stormy convalescence This is especially true since these symptoms interfere with alimentation which results in impaired regeneration and lowering of resistance to the noxious process (see Section V) Occasionally a patient will at first show normal progress toward recovery only to develop alarming symptoms later on and go on to fatal termination

There may be some relationship between the intensity of jaundice and the severity of the disease but this is not entirely reliable (Turner et al) since there is no absolute parallel between the intensity of the icterus and the final outcome Persistence of intense icterus for over two months suggests the development of one of the chronic sequelae Hepatitis may be fatal

in the absence of clinical icterus (Lucke and Mallory 1946)

Pre terminal stage The course preceding fatal termination usually is as follows nausea becomes intractible and vomiting persistent Soon the vomitus and the feces contain blood Skin ecchymoses and petechiae appear and *bleeding from the nasopharynx* and gums may indicate a grave decrease of plasma pro thrombin content Nervous symptoms may precede accompany or follow the above symptoms A mild change in mood or character of the patient may be the earliest sign of im pending hepatic coma For detail of this train of symptoms see page 411

Very rarely grave cardiovascular events de velop which add to or conclude the terminal picture A shock like state may develop with marked hypotension and tachycardia This may be brought on by hemorrhage increase of *vaso depressor mechanism (VDM) by the* damaged liver (p 485) or severe myocarditis (Fig 44b) Massive *hemopericardium* and intra pleural hemorrhage may be a rare cause of death (Eisen and Markovich)

Physical Findings

Jaundice The outstanding physical finding is variable in intensity and may even be absent Thus one of the variants of the disease is hepatitis without jaundice or with hyper bilirubinemia so slight and transient as to escape detection entirely Since this variant depends largely on laboratory findings for diagnosis it will be discussed in greater detail later

The pathogenesis of jaundice is composite *rather than simple* in this disease In the era of catarrhal jaundice the jaundice was assumed to be post hepatic in origin (obstructive or regurgitative) due to obstruction of the com mon bile duct by edema or a mucus plug Now it is clear that parenchymal damage or true hepatitis exists while the extrahepatic bile ducts are free of di ease It follows that the jaundice is at least partially due to a failure of the damaged or destroyed hepatic cells to excrete bilirubin That is the jaundice is of the hepatic type *(parenchymatous)* However occasionally acholic stools and the absence of urobilinogen in the urine result from complete *intrahepatic biliary* obstruction This concep tion is confirmed by the pathologic picture of *the liver Obstruction of the small intrahepatic* bile passages occurs because of exudation edema and *formation of bile thrombi The* jaundice may also be due to leakage of bile from the damaged bile canaliculi

Pruritus is very rare in jaundice of viral hepatitis however, on occasion when it does occur it augments the diagnostic confusion When pruritus is present the jaundice is most likely due to intrahepatic biliary obstruction *rather then parenchymal damage and, hence* the laboratory tests also simulate post hepatic jaundice

In the pre icteric stage some injection of the conjunctivae may be seen and occasionally some hyperemia of the pharynx as well as rhinitis may be present

Barker has called attention to the enlarge ment of the cervical lymph nodes especially *on the right side occurring chiefly*, in the epidemic variety of the disease However, other observers have made no mention of this finding

Liver This organ becomes enlarged in over 50% of cases It may become palpable before jaundice is evident clinically or in the absence of jaundice It may be just palpable below the right costal margin or extend down to the um bilicus Another important finding in the liver is its tenderness The tenderness may be ex quisite or mild *Tenderness on fist percussion* over the liver or on jarring of the patient is a *diagnostic finding*

Variations in the size of the liver can occur from day to day A diurnal variation has been mentioned by Turner and associates In general the liver gradually returns to normal size as the patient recovers However rapid reduction in size without clinical improvement is a bad omen, signifying the development of *acute* yellow atrophy The size of the liver itself at one given time is of *no prognostic significance* for in fatal cases the liver has varied from small to large In general however a signifi cantly enlarged organ accompanies severe disease

The spleen is palpable in 10 or 15% of the

clinical cases however the spleen is enlarged in about 75% of the cases coming to autopsy

Ascites is extremely common in fatal hepatitis and rare in patients who recover Liver damage is usually far advanced and irreversible when ascites develops

Turner and his associates noted ascites in only per thousand of non fatal cases In the cases of fatal hepatitis reported by Lucke *ascites was present in two thirds I have seen* an occasional patient with hepatitis recover in spite of ascites but this finding makes recovery very unlikely

Ascites usually appears abruptly The examiner notices the sudden abdominal distention usually late in the disease several days before death In the patients who recover, the fluid disappears in 1 to 5 days For the pathogenesis of ascites see page 396

Pleural effusion occurs in a considerable number of patients with ascites Edema of the ankles has been noted in about half of these patients but is never marked

Hemorrhagic phenomenon Hemorrhages in the skin and mucous membranes occur frequently in patients who die but only occasionally in the patients who recover The skin hemorrhages are most commonly petechial but occasionally large ecchymoses develop Superficial hemorrhages as well as the hemorrhages from the lower portion of the gastrointestinal tract depend in part on the lowered plasma prothrombin level which in turn depends on the inability of the liver to synthesize this substance in spite of abundant vitamin K Increased capillary fragility is another factor which contributes to the hemorrhagic phenomenon

Esophageal varices in three of Turner s cases were thought to be the cause of fatal hemorrhage Lucke however made no mention of esophageal varices or hemorrhages from them I have seen exsanguinating hemorrhage from esophageal varices in three patients with the chronic sequelae of hepatitis (p 273) This complication would not be expected in patients dying in less than six months

Nervous system findings As has been mentioned symptoms related to the nervous system appear in the late stage of fatal disease The physical findings of hepatic coma are the same in this disease as in cirrhosis (p 411)

I have observed two cases in which persistent tremor appeared during convalescence Since in neither case had the liver damage been marked organic injury of the nervous system seemed unlikely At the time the tremor was present all live function tests were negative and there was no longer any clinical evidence of liver damage *Since atypical tremors and* weakness occur in the psychoneuroses psychiatric consultation yielded the opinion that the tremors were not on an organic basis

Clinical Features—Summary

Symptomatology
- ***Prodromal Stage***
  - **General malaise**
  - **Fatigability**
  - **Aching sensations in extremities**
  - **Anorexia**
  - **Nausea and vomiting occasionally**
  - **Constipation or diarrhea**
- **Icteric Stage**
  - **Chilliness or Chills and fever** } **epidemic form**
  - **Nausea Anorexia** } **severe**
  - **Vomiting common**
  - **Symptoms may subside at height of icterus**
  - **Pain constant aching increased by jarring or cough right hypochondrium**
- **Convalescent Stage**
  - **Appetite improves and becomes ravenous**
  - ***Jaundice begins to fade***
  - **Sense of well being develops**
- **Pre terminal Stage**
  - **Increase of anorexia nausea and vomiting**
  - ***Bleeding from orifices***
  - ***Nervous system symptoms***
  - **Serious cardiovascular symptoms**

Physical Findings
- ***Jaundice***
  - **Variable in intensity**
  - **Absent in 20% of adults and 90% of children**

Conjunctival injection
Enlargement of cervical lymph nodes
Liver—enlarged, tender to palpation *and percussion*
Spleen is palpable in 10 to 15% of cases
Ascites—common in fatal hepatitis
Hemorrhagic phenomenon—involving skin and mucous membranes
Nervous system findings—changes in disposition, tremors delirium, etc (See page 411)

Prognosis

The overall mortality in large groups of cases in both the infectious (IH) and homologous serum hepatitis (SH) over a period of years has been low between 0 13 and 0 44% (Lucke 1944) Thus in the epidemic of homologous serum hepatitis following the use of yellow fever vaccine in 1942 the mortality was about 24% but in the epidemic of hepatitis in our troops in the Mediterranean in 1944 was much higher even though most of these cases were IH type Thus it is unjustified to say that the SH type carries a higher mortality than the IH type Rather is the mortality dependent on the general state of the patient his nutrition and the state of his liver This probably explains the higher mortality in the Mediterranean epidemic because these were combat troops This also at least partially explains the higher mortality in small groups of cases of hepatitis 20% and over (Jersild 1947 Robinson et al 1950 Ratnoff et al 1949) and as high as 34% (Steele 1950) Plasma and blood are given to individuals debilitated by other diseases or surgery and such patients would succumb more readily to another infection In addition to this serum hepatitis is more apt to occur in an older age group which shows a higher mortality but is less susceptible to infectious hepatitis

It has been noted that infectious hepatitis carries a graver prognosis when it occurs in individuals over 45 Alsted (1947) reported a mortality rate of 50% in an epidemic of infectious hepatitis in women over 45 years of age Another group of malignant hepatitis is reported from Sweden predominantly in women over 40 with a mortality of 75% (Salvesen and Lodoen 1950) The wear and tear on the liver from the exigencies of 40 or 50 years of life may account for a higher mortality rate past middle age

We (Baker and Spellberg) reported two patients who developed homologous serum hepatitis following pyloric obstruction due to ingestion of concentrated hydrochloric acid Both patients experienced a prolonged period of vomiting loss of weight and inadequate dietary intake But in spite of this poor nutritional background both of these patients were only mildly ill and recovered quickly and without complications Such examples do not refute the importance of diet in diseases of the liver but rather emphasize the complexity of the problem When we are dealing with a viral or bacterial infection, the final result depends on the virulence of the infective agent as compared with the resistance of the host Perhaps the virulence of this particular virus was low enough so that even the debilitated patients were able to handle it adequately

Hepatitis acquired during the first trimester of pregnancy may affect the offspring We p and Kellog reported the birth of a composite monster under these circumstances The increased demand for essential nutrients during gestation may increase the seriousness of the disease

Prognosis of Post Hepatitic Cirrhosis

The chronic sequelae of viral hepatitis are discussed later (see page 271) Chronic hepatitis as defined below is probably still reversible but post necrotic cirrhosis and cholangiolitic cirrhosis are relentless processes which frequently result in death It is not clear whether these sequelae are the result of continued activity of the virus over a number of years or a result of the morphological disturbance created by the acute disease I think it is more likely the former Cholangiolitic cirrhosis has a course similar to other types of biliary cirrhosis Post necrotic cirrhosis is thought to have a poorer prognosis than portal cirrhosis in view of the poorer response to dietary therapy However some of these patients get along well for years (case 7 p 276)

Sequelae of Viral Hepatitis

The outcome of a patient with acute viral hepatitis consists of one of the following (1) complete recovery (2) death from acute or subacute yellow atrophy or (3) development of chronic liver disease There is no question but that the vast majority recover and only a small percentage of patients die (see Fig 45) The development of chronic liver disease from acute hepatitis was doubted at first because of the pathologic studies of Lucke The clinical observations of Barker and associates Benjamin and Hoyt strongly suggested that the disease may become chronic and the term chronic hepatitis was coined

The chronic sequelae or residuals of acute hepatitis may be classified into three groups (1) the chronic form (chronic hepatitis) lasting 6 months or more (2) the recurrent form (recurrent hepatitis consisting of clinical relapses with or without jaundice due to reactivation of dormant virus or re infection (less likely) and (3) the progressive type with permanent liver damage (Spellberg 1948) The last group may be divided into (a) cholangiolitic cirrhosis (b) portal cirrhosis and (c) post necrotic cirrhosis (Soffer 1934 Watson and Hoffbauer 1946 Spellberg 1948 Kosalka et al 1949 and Post et al 1950)

The frequency of permanent liver damage (Group 3) after viral hepatitis is unknown It is probably no more than 5% and may be considerably less Fernando and Thanabalasundaram found 7 cases of cirrhosis in a series of 14 cases of infectious hepatitis Two of these seven cases may have been nutritional in origin leaving only 5 out of 140 with chronic liver injury

It is my impression that chronic liver disease may follow rather mild even anicteric initial disease which because of its mildness is not diagnosed or treated without bed rest The cases described in some detail below illustrate this point

While the occurrence of true portal cirrhosis following acute hepatitis is disputed by some (Patek 1950) a form of cirrhosis does occur following hepatitis which may be difficult to

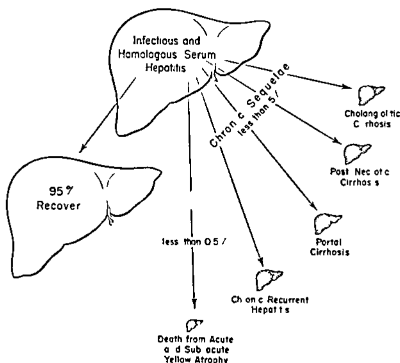


Fig 45 Diagrammatic presentation of the ultimate fate of patients with viral hepatitis

distinguish from true portal cirrhosis The low grade cholangiolitic cirrhosis seems to develop in patients with prolonged or recurrent icterus who at first show little evidence of parenchymal damage This is probably the group that shows pathologically much periportal exudative reaction but little parenchymal necrosis This periportal infiltration fails to resolve fibrosis takes place more interference with patency of bile canaliculi more jaundice and finally esophageal varices and terminal parenchymal failure develop This process may continue for many years

Chronic Hepatitis

Symptoms The term chronic hepatitis is used arbitrarily for those patients with acute hepatitis who do not recover completely within six months Criteria for chronic disease are chiefly clinical but they must be substantiated by some laboratory abnormalities to be objective and dependable

A patient with chronic hepatitis continues to have a palpable liver which is tender to percussion and palpation is productive of spontaneous right upper quadrant pain especially on exercise and complains of anorexia mild dyspepsia especially to fatty foods and increased fatigability However since most of these signs are chiefly subjective a hypochondriacal individual may continue to complain because of his fixation on the right hypochrondrium Objective patients have assured me that after an attack of acute hepatitis they cannot be sure whether the tenderness is real or attributable to the fear of pain

Objective signs If the liver is definitely enlarged or if there is splenic enlargement, the symptoms may be accepted as organic in nature. Mild icterus may persist for a long time and bromsulphalein retention slightly positive flocculation tests and abnormal bilirubin clearance give credence to the diagnosis of chronic hepatitis

The following cases illustrate the post hepatitic sequelae

Chronic Hepatitis Simulating Familial Non Hemolytic Icterus

Case 5 —J G This 23 year old man developed typical infectious hepatitis in September of 1951 Anorexia was of short duration The liver was enlarged 6 to 8 cm below the right costal margin and was markedly tender to palpation and percussion The spleen was palpable

The patient remained at absolute bed rest in the hospital for two months He received a high caloric high protein diet supplemented with intravenous glucose vitamin C and B complex The liver function tests showed gradual improvement (See Table 47) but slight abnormality persisted He was sent home for another month of bed rest Slight tenderness of the liver persisted and the spleen was barely palpable Gynecomastia developed which gradually subsided but slight hyperbilirubinemia persisted In July of 1952 almost one year after the onset of the acute disease the serum bilirubin was 3 3 mg % and the thymol flocculation was 3+

He was hospitalized for liver biopsy The bilirubinemia persisted but the flocculation tests became normal There was no bilirubin or urobilinogen in the urine and there was no bromsulphalein retention In addition an electro

TABLE 47

Liver Function Tests in Chronic Hepatitis Case 4 (above)

Date	Serum Bilirub mg %	Total Prot gm %	A/G	Alk Ph units	Thymol Turb units	Floc	Ceph Chol Floc	Chol Est mg %
9-7-51	11 8	6 8	3 7/3 12	7 5	8 6	4+	3+	160/46
9-1 51	12 9	7 3	3 7/3 6		7 8	3+	4+	130/26
9-17-51	5 6	7 7	3 6/4 1	8 0	1 8	3+	3+	67/44
9-25-51	3 7	8 15	3 9/4		11 1	2+	4+	56/60
10-6-51	9	8 3	3 6/4 7	6 0	9 1	3+	4+	195/61 6
11 1-51	0	8 15	4 5/3 9	4 1	8 5	+	+	17 /72
3-25-5	5	7 8	5 0/ 8		0 8	+	1+	115/68
7-2 -5	35	8 1	5 /2 9		1 8	3+	0	163/ 4
8-12-52	1	7 5	5 2/2 3	1 8	3 0	1+	3+	116/82
3-30-53		7 7	4 7/3 0		2 0	1+	0	17 /72



Fig 46 Needle biopsy of liver (X 100) showing normal architecture except for slight increase of portal round cell infiltration. Seven months before persistent icterus. Laboratory tests: Table 47 (see page 7)

phoretic study of the serum proteins showed normal partition. The liver biopsy showed normal histology (Fig 46)

The isolated finding of hyperbilirubinemia suggested constitutional hepatic dysfunction or non hemolytic icterus but the absence of this trait in members of his family plus the unquestionable acute hepatitis places this case in the category of a chronic hepatitis with an isolated retention of bilirubin. Apparently the renal threshold for bilirubin likewise increased since the one minute (prompt reacting) fraction was over 1.0 mg % but there was no bilirubinuria

Post Necrotic Cirrhosis

The following patient illustrates the development of one of the most serious sequelae of viral hepatitis as well as the confusion that may arise about the exact classification of chronic liver disease

Case 6 — Male age 3? This patient entered the hospital in April 1945 because of severe right upper abdominal pain aggravated by exertion and jarring. The pain on several occasions became severe enough to require narcotics. His appetite was good and he lost no weight. He was able to carry on his occupation as a mail clerk until he entered the hospital

The past history included a brief illness while in service in May 1944 for which he was hospitalized for several days with a diagnosis of pneumonitis. At that time he had a low grade fever and pain in the lower right side of the chest aggravated by coughing. Three months prior to this illness (February 1944) he was vaccinated against yellow fever

Physical examination in 1945 was negative with the exception of a liver palpable about 6 cm below the costal margin and on the anterior surface an oval shaped egg size soft nodule was palpable. The liver was tender to palpation and percussion

Because of this palpable nodule surgical



F g 47 A M ophotograph of sect on of l er (× 85) of pa nt approx ma el one y a er acu e h pa t t s Shows th n strand of fib ous ue mononu lear cell nfil a on and mul pl ca on of b le duct In pre ed a ea l po al c rrho (ca e 6)

B Low power (× 5) of sec on of l ver of same pa ent a n F g 48 n 95 e en and on half ea s af attack of hepat how ng t p cal la ge nodules of po nec o c c rrho Labora o y da a tab e 48 h o page 7

explorat on vas done to rule out a hepaton a Tl e l ver pre ent d the g os appearance of portal c rrhos and a b ops revealed per po tal fibro s round cell nfiltr tt n and b le du t mult pl cat on nterpreted as portal c rrl o s Th s a reported b me as an nstance of portal c rrho s follow ng hepat t (Spellberg 1948—F g 4 a)

The pat ent va followed ever t o t three nonths unt l 195 when he was not seen to about ne year He re entered the l o p tal n No embe 195 w tl edema jaund ce and marke l a c tes Tl e l er vas palp Lle S cm l elo the costal marg n an l tl e spleen as palpable n sp te of a c te

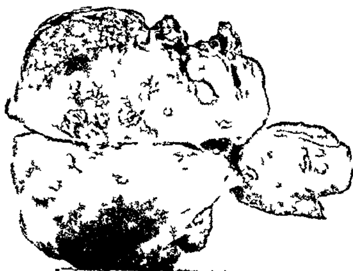
A compar o of the l ver funct on te t n 1946 and 1951 s g ven n Table 48

The pat ent va kept ar al olute l ed re t and g en a h gh prote n d et tl upple mentar v tan n and n etl on ne He eeme l to n pr e Al o t three eeks af er entrance to the ho p tal he de eloped a ma e hemo rhage fron a r pt red e of l ageal ar x lu ng the n gl t an l l ed l efore e ph geal tan ponade co ld l e n t tuted Autop re eale l a c arse nodular (po t nec ot c h l oth gr sl a l l tol g call (F g 47b 48

TAB 48

Li Func n Te n a l a n w h Po N r C h (F c 5 p 7 76

D	T	P gm		B mg	b	Th m	b	B P	C ph Ch F	k m	F	t	Ph ph se
6–2 46		6	4 3	8			6	%	+				
1	5	5 8		b	8 o		7		4+	4	60%		8 Bod n k L



F g 48 l o n m c ci h N m l k h pe f n d n gh l be and a n ph f l f l be l ghed 400 gr m M g ng 4 b

TAB 49

l F n n Te a P n W h P N r C rrh s R pond ng o Th p ca 6 p e b

	T F at gm	B mg	b	Thymol Tur	F at	F	kk kn	P	P otk T
4 5		6 4		o 8	4+	3+	4 6 4%	6	6 5 sec BSI
9–		8	o 8	8	+	+	8 —%	o	6%
4	6 8	6	o	4 o	o	+	46 4%	o	3%

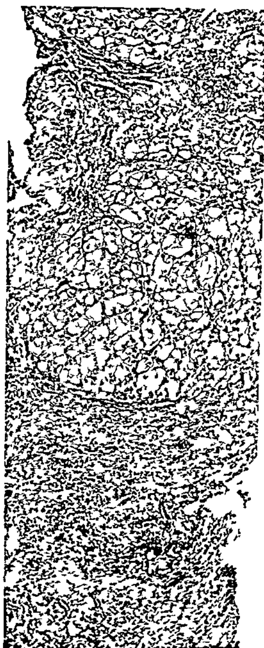


Fig 49 Microscopic section of needle biopsv (× 100) showing post necrotic cirrhosis Large band of fibrous tissue (collapsed reticulum) mononuclea cell infiltration reduplication of bile ducts Hi tor, p ge 76 laboratory data Table 49

This patient illustrates the following points of interest (1) A mild hepatitis (probably homologous serum due to vaccine) undiagnosed in 1944 (2) inadequate bed rest led to (3) chronic liver disease one year later, (4) biopsy in 1945 suggested portal cirrhosis, (5) patient was carrying on with his normal activities for over six years and (6) died 7½ years after the original attack of hepatitis from esophageal varices hemorrhage preceded by hepatic failure (7) at autopsy the cirrhosis was of the post necrotic rather than the portal type

Not all patients with post necrotic cirrhosis fare so badly although all of them should be watched for the treacherous esophageal varices and liver failure

Case 7—Male age 48 This patient developed infectious hepatitis in 1945 He rested in bed less than one week! In 1951 he developed epistaxis due to hypoprothrombinemia ascites and edema His liver function tests were markedly abnormal (Table 49) and the liver biopsy showed histologic changes compatible with post necrotic cirrhosis (Fig 49)

After prolonged bed rest extending for almost one year, his liver function tests are normal and he is carrying on his occupation in 1953 two years after the appearance of signs of chronic liver disease Edema and ascites are absent

Cholangiolitic Cirrhosis

Some patients who have very few clinical symptoms during the acute stage of hepatitis are especially likely to remain undiagnosed and fail to receive proper therapy This is seen most frequently in young individuals who develop the exudative pericholangiolar process with minimal parenchymal necrosis These patients are apt to have prolonged and persistent icterus with a minimum of other complaints The condition may be confused with post hepatic jaundice such a group of patients

TABLE 50

Liver Function Tests in Post Hepatitic (Cholangiolitic ?) Cirrhosis F age 16 (cas 7 page 78)

D t	T t l P t gm %	A/G	B l b mg %	Thym l T b t	Fl	C C F	Ch l Est	Alk Ph t	
4- 4-50	9 1	3 1/6 0	9 9	8 1	4+	3+	116/55%	11 2	
10-13-50	8 8	4/6 4	5 9	5 7	3+	3+	118/36 5%	17 7	Biopsy
5- 3-51	9 6	2 1/7 5	3 3	6	+		60/31 4%	13 9	Biopsy
			Clob—α 1 1 β 95 γ 3 45						
1-11-5	8 1	5/5 6	9		+		1 6/64%	31 9	Biopsy

Alkaline phosphotase in Comori u

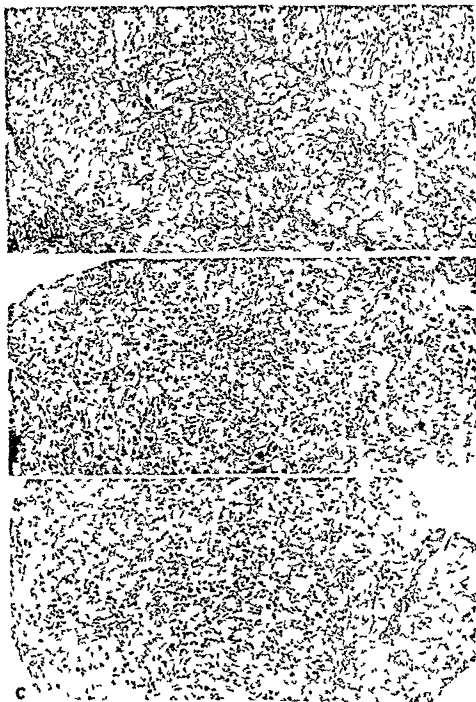


Fig. 50 Seri[illegible] b[illegible] from a female patient age 16 with chronic sequelæ of hepatitis sh[illegible] w[illegible] p[illegible] re[illegible] improvement

A Obt[illegible]d [illegible]

B Obt[illegible]ed [illegible]

C Obta[illegible]ed [illegible]

Labo[illegible] Tabl[illegible]

was clearly described by Watson and Hoffbauer

The following patient may fall into this group because of the persistent icterus minimal symptoms and slow improvement

Case 8—Female age 16 (A D) This patient entered the hospital because of jaundice of several weeks duration Epistaxis and malaise were noted three months before There was mild anorexia with only several pounds weight loss in three months

Icterus was distinct but the liver was palpable 2 cm below the right costal margin and was only slightly tender The liver function tests (Table 50) show gradual improvement over a two year period The icterus still persists but is much decreased and serial biopsies have likewise shown gradual improvement (Figs 50a b c)

39—Viral Hepatitis Laboratory Features, Diagnosis, and Treatment

Laboratory Features

The laboratory is of some assistance in the diagnosis of the disease and of considerable assistance in following its course and clarifying the pathologic physiology involved

The old theory that the disease is one of obstruction of the common duct by edema or mucous plugs is invalidated by the fact that the functional impairment of the liver develops early in the disease

Serum Bilirubin

In anicteric and preicteric hepatitis there is an increase of urinary urobilinogen and sometimes of urinary bilirubin These simple tests of urinary pigments have again been proposed as screening tests for early and subicteric cases of hepatitis (Swift et al 1950) When the jaundice has persisted for a long time albumin may appear in the urine as a result of tubular irritation When obstruction of the intrahepatic bile ducts becomes marked the urobilinogen disappears from the urine and the stools become acholic this persists for only a short period of time (from 7 to 10 days)

Hyperbilirubinemia varies greatly and although it sometimes parallels the severity of the disease this is not always the case The serum bilirubin shows a rapid decline early in convalescence but a mild persistent hyperbilirubinemia may persist for a long time (p 7) This is in keeping with the tendency of the bilirubin excretion test to remain positive for a long time after recovery from the disease

Serum Iron

The serum iron level rises above normal early in acute hepatitis and persists after the hyperbilirubinemia has subsided (Peterson 195) (Fig 51)

Flocculation Tests

The cephalin cholesterol flocculation test becomes positive early frequently before icterus appears and is positive in the anicteric type of disease It may continue mildly positive after the patient has apparently recovered and indicates persistence of liver disease While the cephalin flocculation test is probably the most sensitive flocculation test in the early stages of the disease the thymol turbidity and floccula

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Serum Proteins

Changes in serum protein are detectable early by using the electrophoretic method of analysis By using a chemical method for fractionation of serum proteins (p 26) we have shown (Spellberg Cohn Wolfson 1950) that the rise of gamma globulin i an early and very sensitive test for hepatic dysfunction and occurs early and remain positive late in convalescence (Table 51) A marked drop in albumin and rise in gamma globulin i e increase in gamma globulin/albumin ratio has a grave prognostic significance (Spellberg et al 1950)

Bromsulphalein Clearance

Bromsulphalein clearance is a useful test in the anicteric form of the disease or after the icterus has subsided Bromsulphalein clearance i accelerated if the test is done post cibum There i a relationship between the degree of hyperbilirubinemia and dye retention during the active phase of the disease Early in the disease or during the prodromal period and late in convalescence considerable bromsulphalein retention may be present with minimal or no icterus (Havens et al 1950)

Hippuric Acid Test

The hippuric acid synthesis test is also of value The intravenous test i probably more

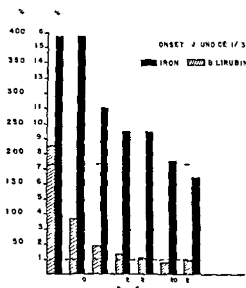


Fig 51 Th r t th er m ir n and the serum bil b n in prese tat ca e of acute h pat t s (From J Pet r n L b Cl n Med 9 5 19)

accurate than the oral test In the latter nausea and vomiting interfere with absorption and impair the validity of the test This test frequently shows impairment of function in hepatitis

Prothrombin Time

The prothrombin content of the serum i depressed infrequently when the liver is unable to synthesize it Severe lowering of the plasma prothrombin is a serious signal Bleeding from various orifices and ecchymoses may occur at this point Vitamin K administration is ineffectual

Cholesterol

The total serum cholesterol is usually normal (Gardner et al 1950) However it may be slightly elevated during the stage of intra hepatic obstruction A marked fall in total cholesterol may indicate a serious prognosis The cholesterol esters are usually depressed especially during the period of jaundice and rise rapidly during convalescence (Table 51) A drop of cholesterol esters to low level i considered a grave prognostic sign however I have seen patients recover with cholesterol

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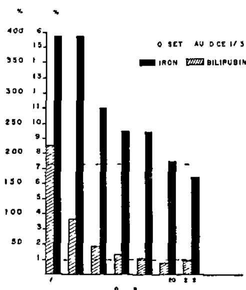


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tion may add to the number of positive tests Moreover during convalescence and chronicity the thymol turbidity and especially the thymol flocculation may remain positive after the cephalin flocculation returns to normal Therefore it is advisable to use both of these tests The thymol turbidity and cephalin cholesterol flocculation tests are especially useful in detecting the anicteric form of virus hepatitis (Denber and Leibovitz 195) It is also worth mentioning that the thymol turbidity test is more strongly positive in viral hepatitis than in nutritional cirrhosis This is undoubtedly dependent on a characteristic hyper gamma globulinemia which is peculiar to inflammatory liver diseases (Kunkel) The colloidal red test usually does not exceed the diagnostic accuracy of the other flocculation tests (Neefe et al 1950)

Serum Proteins

Changes in serum proteins are detectable early by using the electrophoretic method of analysis By using a chemical method for fractionation of serum proteins (p 26) we have shown (Spellberg Cohn Wolfson 1950) that the rise of gamma globulin is an early and very sensitive test for hepatic dysfunction and occurs early and remains positive late in convalescence (Table 51) A marked drop in albumin and rise in gamma globulin i e increase in gamma globulin albumin ratio has a grave prognostic significance (Spellberg et al 1950)

Bromsulphalein Clearance

Bromsulphalein clearance is a useful test in the anicteric form of the disease or after the icterus has subsided Bromsulphalein clearance is accelerated if the test is done post cibum There is a relationship between the degree of hyperbilirubinemia and dye retention during the active phase of the disease Early in the disease or during the prodromal period and late in convalescence considerable bromsulphalein retention may be present with minimal or no icterus (Havens et al 1950)

Hippuric Acid Test

The hippuric acid synthesis test is also of value The intravenous test is probably more

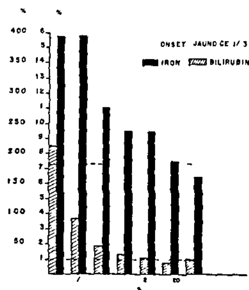


Fig 51 The c r e t th erum iron nd the se m bilr b i pr entati e ca f ac te hepatit s (From J Peter o I b Cli M d 39 5 195)

accurate than the oral test In the latter nausea and vomiting interfere with absorption and impair the validity of the test This test frequently shows impairment of function in hepatitis

Prothrombin Time

The prothrombin content of the serum is depressed infrequently when the liver is unable to synthesize it Severe lowering of the plasma prothrombin is a serious signal Bleeding from various orifices and ecchymoses may occur at this point Vitamin K administration is ineffectual

Cholesterol

The total serum cholesterol is usually normal (Gardner et al 1950) However it may be slightly elevated during the stage of intrahepatic obstruction A marked fall in total cholesterol may indicate a serious prognosis The cholesterol esters are usually depressed especially during the period of jaundice and rise rapidly during convalescence (Table 51) A drop of cholesterol esters to low levels is considered a grave prognostic sign however I have seen patients recover with cholesterol

TABLE 51

Liver Function Tests in a Patient with Homologous Serum Hepatitis

Date	Total Protein gm /100 cc	Albumin	Alpha	Globulin Beta gm /100 cc	Gamma	Phosphatase*	Serum Bilirubin mg %	B S P	Cholesterol Total mg	Esters	Ceph Floc	Thymol Turb units	Floc
8-5-48	6 7	2 3	0 8	1 3	2 3	25 5	12 4		24	5 2	3+	25	4+
8-19-48	7 8	7	1 6	1 1	4	14 5	4 4		254	62	2+	6 4	0
8-26-48	7 6	3 3	1 4	1 05	05	13 5	3 0		1 9	60	3+	8 6	1+
9-29-48	7 8	3 7	1 4	0 75	1 95	20 2	1 2		197	70	4+	8 1	2+
11-28-48	7 1	3 8	1 1	0 7	1 5	15	0 5	1 0%	177	60	3+	4 2	0
12-10-48	7 5	3 9	1 6	0 95	1 05		0 4		22	70	+	4 0	0
3-17-49	6 6	3 4	1 5	0 8	0 9	11 3	0 3	1 0%	256		0	3 6	0

* Pho phatase are in Huggins units normal value up to 15 units

esters of 0 and some of these were not very ill clinically

Alkaline Phosphatase

The serum alkaline phosphatase rises especially during the period of intrahepatic biliary obstruction Rapid or marked decrease of alkaline phosphatase in spite of continued biliary obstruction and rising serum bilirubin is a poor prognostic sign

Cholinesterase

Serum cholinesterase level determinations are considered useful in following the course of viral hepatitis (Vorhaus and coworkers) The *usefulness of this test in hepatitis is disputed* by others (Sborov and Keller)

Hemogram

There are no distinctive hematologic features *in this disease The erythrocyte count and* hemoglobulin are usually well sustained except in serious and fatal disease in which anemia develops The leukocyte count is usually normal or low but occasionally leukocytosis develops *The differential count is usually not* remarkable but the lymphocytes may predominate A large number of target cells have been reported in this condition

Cholecystogram

Gallbladder visualization w[illegible] is without danger and may be a[illegible] during the period of icterus Th[illegible] visualized in the ma[illegible] serum bilirubin be[illegible] dose of dye may b[illegible] 1950) But the in[illegible] *zation may be impaired after the patient is free* of icterus and has apparently recovered Non visualization of the gall bladder was stressed by Barker in patients with chronic hepatitis Early in the disease at least failure to visualize *the gall bladder is due to inability of the liver* to excrete the dye There is a question however whether the gallbladder itself may become involved Disturbances in the chemical constituents of the bile may favor the formation of *cholelithiasis*

Gastroscopy

A picture compatible with superficial and mild hypertrophic gastritis was described on *gastroscopic inspection of the gastric* mucosa (Knight and Cogwell 1945 Monat et a 1946 and Loughead and Golding 1952)

DIAGNOSIS

The diagnosis of homologous serum hepatitis is aided by a history of exposure to blood or blood products or inoculation Infectious hepatitis may be suspected if exposure to other cases i known During an epidemic the disease *should always be suspected* The onset with malaise anorexia gastrointestinal or mild respiratory symptoms is characteristic Pain in the region of the enlarged liver is *dull and* aching and the tenderness of fist percussion is typi[illegible] disease The jaundice varies in [illegible] ritus is absent *If the labora* tory [illegible] parenchymal damage and the [illegible] *is normal or low* the diag nosi[illegible] The complexity in diagnosis ar[illegible] hat may begin with [illegible] pain simulating bili[illegible] ion tenderness

over the liver and show laboratory data compatible with post hepatic jaundice Liver biopsy may be of help in such instances (Fig 16)

Differential Diagnosis

The differential diagnosis of hepatitis is really the differential diagnosis of jaundice (Section III) The most important disease to exclude is choledocholithiasis If the hepatitis is of the cholangiolitic type that is intra hepatic biliary obstruction predominates and hepatocellular damage is minimal liver biopsy or even surgery may have to be resorted to for exclusion of a common bile duct obstruction Cholangiography is helpful during surgery

Portal cirrhosis may have to be considered in the differential diagnosis This chronic disease is common in an older age group the onset is more insidious and there is a history of alcohol ism and or malnutrition Spider nevi and the hard non tender liver help to confirm the diag nosis of cirrhosis The spleen is more commonly enlarged and esophageal varices may be present The flocculation tests which are usu ally strongly positive in hepatitis are only mildly positive or negative in cirrhosis

The anicteric form of hepatitis frequently masquerades as influenza and has to be differ entiated from all the other lowgrade febrile illnesses

The differential diagnosis of the chronic sequelae post necrotic cirrhosis and cholangio litic cirrhosis from portal cirrhosis is very diffi cult pathologically and may be impossible clinically This differentiation is of academic rather than practical interest since the treat ment is the same The following point may be of help The post hepatitic cirrho is occurs at a younger age it dates back to an acute illness with fever and jaundice the flocculation tests are apt to be more strongly positive a history of malnutrition or alcoholism is lacking The liver biopsy may be of help by showing a lack of fatty change more marked exudative process and broad strand of fibrous tissue

Prophylaxis

Sanitation

The prevention of the naturally occurring disease depends largely on sanitary conditions because contamination of water milk and food supply appears to be an important route of transmission Since droplet infection is also a possibility care should be exercised in avoiding direct contact as is done in upper respiratory tract infections Because the virus is found early in the disease quarantine is impracticable since it would have to be instituted before the diagnosis is established This is especially true in infant epidemics in whom the disease is generally anicteric and may remain sub clinical in half of the patients (Bennett et al 1952)

Sterilization of Blood Products

Prevention of homologous serum hepatitis involves avoiding the use of blood or serum from a person who may be harboring the virus Since the virus may remain in the circulating blood for long periods it is best to exclude as donors all persons giving a history of jaundice at any time This will not prevent occasional use of icterogenic serum because the disease may be in the incubation period at the time the blood is drawn Using as few donors as possible for serum pools will reduce the incidence of infection

Needles and syringes should be sterilized by autoclaving and boiling to assure destruction of the virus

Sterilization of plasma by ultraviolet light has been introduced by Wolf and coworkers (1947) and Stokes and coworkers (1948) Re ports of serum hepatitis occurring after use of plasma treated by this means have appeared in the literature (Janes et al Barnett et al Rosenthal et al 1950) This means of sterili zation is not applicable to blood Destroying the virus by means of nitrogen mustard has been suggested (Hartman et al 1949) This is applicable to blood The simple means of sterilization by exposure to room temperature for three to six months suggested by Allen and coworkers (1950) is a simple measure Com bined ultraviolet exposure and storage at room temperature should increase the likelihood of destroying all the virus

Gamma Globulin

The efficacy of gamma globulin administra tion in prevention of infectious hepa i is has

been established. Stokes and Neefe early in 1945 reported intramuscular injection of 0.15 cc. of gamma globulin per kilogram of body weight in 53 persons who were exposed to an epidemic of infectious hepatitis in a summer camp. A group of other persons uninoculated were used as controls. Hepatitis developed in about 70% of the controls but in less than 20% of inoculated persons. The usefulness of gamma globulin in prophylaxis has been corroborated by Capps, Bennett and their coworkers (1952). The incidence of the disease in nurses who received 0.06 cc. of gamma globulin per pound (approximately 0.15 cc./kilo) of body weight was sharply reduced as compared with the non-inoculated group. The duration of the immunity in some suggests that active immunity was produced by the aquisition of a subclinical infection in a partially (passively) immune individual. It has been suggested that a very mild anicteric form of hepatitis may develop in some individuals who receive the gamma globulin late in the incubation period; when given early, complete but brief immunity is produced.

It has been suggested that gamma globulin affords protection against homologous serum hepatitis as well. Grossman, Stewart and Stoke made a study at one army general hospital where many cases of post-transfusion hepatitis were seen. One group of unselected subjects received an injection of 10 cc. of globulin and a second group 10 cc. one month later. Among the inoculated group the incidence of hepatitis was 0 to 4%, while among untreated controls the incidence was 7.7 to 13.1%, a significant difference. Considerable doubt exists about the prophylactic efficacy of gamma globulin in homologous serum hepatitis.

Active Immunization

Active immunization is more desirable than passive immunization. A provocative observation was made by Drake and associates which seems to point the way. Skin testing for infectious hepatitis was done in about one fourth of the inmates of a closed institution which was the seat of an epidemic of the disease. Only five cases of hepatitis developed among 320 skin tested individuals. Four of these cases developed among 176 skin test negative subjects who were presumably susceptible at the time of the test. In contrast, 112 cases of the disease developed in 825 non-skin tested individuals or almost 10 times as many as among the tested individuals. This observation is at least suggestive of the possibility that the minute amount of antigen used in the skin test material has provoked the development of immune bodies against the virus.

Prophylaxis—Summary

Infectious Hepatitis

1. **Improved sanitation**
2. **Proper handling of excreta**
3. **Gamma globulin—0.15 cc. per kilogram of body weight**
4. **Active immunization—a goal for the future**

Homologous Serum Hepatitis

1. **Careful screening of donors**
2. **Sterilization of syringes and needles with heat**
3. **Sterilization of plasma by**
   a. **ultraviolet light**
   b. **storage at temperature of 80° F.**
   c. **nitrogen mustard**

TREATMENT

Bed Rest

One of the most important agents in the treatment of viral hepatitis is bed rest. Absolute bed rest should be enforced for at least a month and ambulation should be carried out cautiously, depending on the clinical picture, size and tenderness of the liver and liver function tests. When ambulation results in an increase in size and tenderness of liver and a deterioration of liver function tests, further bed rest should be instituted. The four cases of chronic sequelae described above (p. 27[illegible]) had insufficient rest during the acute stage of the disease. This is one of the most important factors contributing to chronicity.

The suggestion by Swift et al. (1950) that ambulation may be allowed when the serum bilirubin is 3.0 mg. per 100 cc. or below is dangerous in view of the fact that fatal hepatitis may be anicteric or show mild jaundice.

Diet

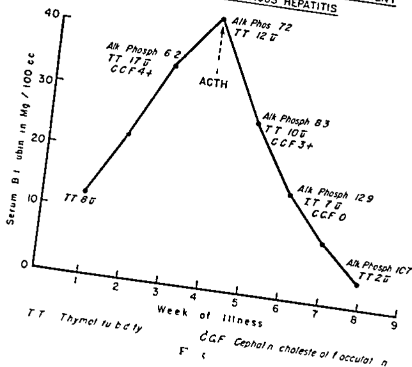
Diet must be adequate especially in proteins carbohydrates and vitamins Total calories are so important that fats should be included to make the diet attractive and palatable The dispute about the amount of fat in the diet is academic since many patients with hepatitis avoid fatty foods The ideal dietary intake would be 350 to 450 gm of carbohydrates 150 gm protein and fat as desired or needed for palatability This would require supplementation with sweetened and protein fortified drinks (p 574 Table 75)

Alpha tocopherol 100 mg three times daily orally is worth using in view of the anti necrogenic effect of this vitamin in nutritional liver injury in animals (p -9)

The use of lipotropic substances such as methionine or choline cannot be defended on the basis of the pathology of this disease since fatty metamorphosis is usually not seen However since fatty changes may precede the development of hepatitis or accompany it because of nutritional disturbances (Fig 43a) these harmless substances should be used especially when food intake is inadequate (for other details see p 311)

Aureomycin has been proposed and used in the treatment of hepatitis Its administration by mouth it is contended decreases or changes bacterial flora which results in a reduction of fermentation and of byproducts toxic to the liver There is also a possibility that the aureomycin acts as a virocidal agent It was originally proposed for use in hepatic coma (Farquhar et al 1950) We have not found it particularly effective nor are the reports in the literature impressive It has a disadvantage since by producing nausea it may interfere with food intake Aureomycin as well as terramycin may produce fatty and other degenerative changes in the liver (p 177)

Cortisone and adrenocorticotropic (ACTH) hormones have been used in the treatment of various forms and stages of hepatitis In spite of the theoretical contraindications to its use



F   c

we must not close our eyes to its possible usefulness in selected cases. Since viral hepatitis is a disease with a very high recovery rate and low mortality, it is difficult to establish objective criteria for the usefulness of a new therapeutic agent.

Bluemle and associates treated one patient with chronic hepatitis with ACTH. This patient developed malaise and ascites during the treatment. Diuresis and decrease of icterus followed discontinuance of this hormone. Thorn and associates place hepatic diseases in the group of diseases in which ACTH therapy is of questionable value, although they report favorable results in one case of serum hepatitis. Ducci and Katz found this hormone effective in conjunction with aureomycin in two cases of hepatitis in hepatic coma. Colbert and associates found 100 mg. of ACTH daily in divided dose continued for 9 to 21 days effective in the treatment of five patients with viral hepatitis. They noted a recurrence of symptoms and arthralgias upon early discontinuance of the drug. Untoward effects consisted of glycosuria, edema, ascites and hypertension. Rifkin and associates found clinical improvement in four patients with homologous serum hepatitis after administration of ACTH and cortisone.

I have seen these drugs used in mild or moderately severe hepatitis in which recovery would be expected with the conventional therapeutic measures. The recovery of these patients is no proof of the efficacy of these hormones. In one very ill patient with homologous serum hepatitis, superimposed on ulcerative colitis, cortisone was ineffective and the patient died. Another 27 year old male patient with very severe hepatitis with a large tender liver and persistent anorexia and vomiting who required parenteral fluids for sustenance showed very rapid improvement with development of a hearty appetite, decrease of liver tenderness and improvement of liver function tests upon institution of ACTH therapy (Fig. 5.)

The chief source of usefulness of this hormonal therapy is the improvement of appetite and the euphoria that it produces. Reduction of hyperbilirubinemia, reduction of hyperglobulinemia and improvement of other liver functions tests have been observed. One must watch for water and salt retention when using these substances. The salt intake should be curtailed and potassium salts given by mouth.

VII The Role of Diet in Liver Disease

40 — *Dietary Factors Implicated in Liver Injury*

Lipotropic Substances

One of the most important advances in our knowledge of liver disease and indeed one of the most significant advances in medicine as a whole in the past 30 years deals with the study of the role of diet in the pathogenesis of hepatic injury. It is interesting to note that this new and fertile approach to one of the riddles of medicine began at the same time and as a by product of one of the leading medical discoveries of this century namely insulin. As recently as 1934 Moon in his comprehensive review of the pathogenesis of cirrhosis made only passing reference to diet as a cause of increased susceptibility of animals to certain poisons. However in 19 4 Davis reported on the protective effect which carbohydrates have against experimental carbon tetrachloride poisoning.

The modern era of the study of the nutritional aspects of liver disease dates back to the observations of Allen and his coworkers in 19 4 that depancreatized dogs kept alive with insulin developed fatty livers which were preventable by feeding raw pancreas. This in turn led to an analysis of the factors in pancreas which were responsible for the prevention of this type of fatty liver. This resulted in two divergent viewpoints about the factor supplied in the raw pancreas and therefore deficient in these animals namely 1 that the missing factor is a dietary constituent and 2 that the missing factor is a hormone.

Choline

The Toronto group developed the evidence that the missing factor is a dietary constituent. First it was pointed out by Hershey and Hershey and Soskin that substitution of lecithin for raw pancreas was effective in preventing this type of fatty liver and later Best and coworkers found that choline was the active part of lecithin. Thus the lipotropic effect of choline was established.

The lipotropic effect of choline also stems from another group of observations on the rat. When this animal was placed on a low protein (1 5 %) and high fat diet a markedly fatty liver developed. This could be prevented and cured by addition of lecithin or choline to the diet (Best, McHenry, MacKay). The lipotropic effect of added protein (casein) was therefore thought to be due to its choline content. Analogues of choline betaine and methionine were also found to have a lipotropic effect probably by virtue of their change into choline in the body.

Lipocaic Lipotropic Hormone?

Dragstedt and his coworkers at the University of Chicago presented some experimental evidence which suggested that the fatty liver in depancreatized dogs was due to the loss of another pancreatic hormone besides insulin rather than a dietary substance. They called this hypothetical hormone lipocaic. Their ex

periments showed that while depancreatized dogs developed fatty livers ligation of the pancreatic ducts or removal of external pancreatic secretion by fistula did not result in hepatic abnormality This seemed to indicate that the absence of the external pancreatic secretions was not responsible for the pathogenesis of fatty livers They obtained an extract of pancreas 100 gm of which yielded 1 8 to 2 5 gm of active substance One to one and a half grams of this extract (lipocaic) administered daily prevented fatty livers in depancreatized dogs Lipocaic according to this investigation did not contain sufficient choline to account for it activity likewise extracts of other organs prepared in a similar manner and containing just as much or more choline were ineffective

This experimental evidence was challenged by several groups of investigators Best and his coworkers were able to prevent and cure fatty livers in rats on a low protein diet by means of this hormone however they maintained that the dose used contained sufficient choline to account for its action and there was no need of attributing hormonal properties to this extract Montgomery and Chaikoff were able to produce fatty livers in dogs by ligating the pancreatic ducts as well as by a complete pancreatic fistula They therefore attributed this type of fatty liver to loss of pancreatic enzymes They varified this assumption by preventing and curing these fatty livers by administration of activated pancreatic enzymes by mouth Ligation of the pancreatic duct in rats has also produced fatty livers and this was cured by administration of pancreatic proteolytic enzyme (Clowes and MacPherson)

It became apparent that the fatty livers of rats on low protein diets as well as those of depancreatized dogs were dependent on a deficiency of choline In one case it was due to a deficiency in the food (low in protein) and in the other it was due to poor digestion and lack of absorption of proteins The pancreatic enzymes administered to dogs aided in absorption of the choline present in the food The extract of pancreas called lipocaic either supplied choline or pancreatic enzymes or both and thereby produced its lipotropic action

Role of Vitamins in Production of Fatty Liver

Thiamine

The production of fatty livers by choline deficiency could be retarded by a low thiamine diet and hastened by increasing the thiamine intake The term 'thiamine fatty liver' was therefore applied to this condition (MacFarland and McHenry) This effect of thiamine is probably due to two distinct actions It inhibits cholinesterase activity, and therefore acetyl choline remains intact and less free choline is available also thiamine may stimulate conversion of glycogen into fat in the liver

Inositol and Biotin

Other types of experimental fatty livers are due to deficiency of inositol and increased amounts of cholesterol in the diet The development of a fatty liver in the depancreatized dog has been accelerated by the feeding of meat extract which is presumably due to its content of biotin (Ralli and Rubin) McHenry has referred to this as the biotin fatty liver and claimed that this type of fatty liver can be prevented by inositol The lipotropic propertie of inositol have been questioned by others (Sellers et al 1948) The fatty liver produced by the high cholesterol diet is referred to as the cholesterol fatty liver

Other Dietary Factors Responsible for Fatty Livers

Fatty livers have been produced in female rats by the use of ethionine a metabolic antagonist of methionine These fatty livers are preventable by methionine and glucose but not by other amino acids Deficiencies of various other amino acid have likewise resulted in fatty livers Tryptophan (Adamstone and Spector 1950) leucine (Maun et al 1945) threonine and lysine (Dick et al 195) deficiencies have resulted in fatty livers while phenylalanine and histidine deficiency (Maun et al) has not We have produced fatty livers in guinea pigs by diets containing 20% butter fat but apparently adequate in other respects The substitution of hydrogenated vegetable fat for butter fat reduced the severity of the fatty livers (Spellberg et al Figs 53 54) Differences

Fig 53 Microscopic section (Sudan III stain) of markedly fatty liver in guinea pig produced by diet r m an Note the gr t am t of fat in the periphery of l b le (Spellberg and Keet)

in reactions to different types of fat have been observed by others (Gyorgy) Feeding of a high fat diet has resulted in fatty liver in dogs (Chaikoff et al 1943)

Mode of Action of Choline

Because choline forms an integral part of the phospholipid molecule it was assumed that this substance acts by stimulating phospholipid synthesis It was also thought that choline administration results in increased transport of fat from the liver in the form of phospholipid (Bloor) More recently Zilversmit and coworkers (1948) by using tagged choline noted that it increased phospholipid turnover in the liver but not in plasma They concluded that the lipotropic action of choline is dependent upon increased utilization of phospholipid by the liver rather than increased transport from the liver to peripheral tissues

The lipotropic property of proteins depend on their content of choline and choline precursors except in the cases of other specific amino acid deficience Methionine and betaine



Fi 54 D tar f tt cirrh g n p e (From Spellberg and Keet n Am J M Sc 2 682 1949)

are lipotropic agents by virtue of their convertability into choline The ethionine fatty liver is an exception to this since only methionine but not other lipotropic agents prevents it It should be emphasized that choline and its precursors are effective only in choline deficiency fatty livers and are ineffective in other types of fatty livers The fatty livers produced by specific essential amino acid deficiencies mentioned before respond only to these specific substances

Morphologic Changes in Experimental Fatty Livers and Their Relation to *Cirrhosis*

The experimental production of fatty livers is of interest to the clinician not only because of the clinical importance of fatty livers but especially because of their possible relationship to cirrhosis

It is worth while to recount the description given by Best and his co workers of the steps in the development of the choline deficient fatty liver This type of fatty liver has been subjected to the most exhaustive and pains taking studies Evidence of choline deficiency appears within 24 hours after the animal is placed on the deficient diet The first deposits of excess liver fat are seen in the central portion of the lobule around the central vein and consist of small intracellular globules At the end of one week all the liver cells are markedly distended with fat As the fat accumulates the small globules of fat coalesce distending the cell with a large pool of fat compressing the nucleus against the cell wall Eventually the cell membrane is distended to its limits and ruptures Two adjacent cells on rupturing form a common pool of fat or a so called fatty cyst These are joined by more ruptured cells thus large fatty cysts are formed The fat is no longer intracellular but extracellular and intercellular As would be expected these pools of fat eventually rupture into bile canaliculi and sinusoids When the cysts empty into these channels the cyst wall collapses and accounts for the strands of fibrous tissue which is really an accumulation of many flattened and compressed cells consisting of a mass of nuclei with little cytoplasm This may be the beginning of dietary cirrhosis

This discharge of fat into sinusoids may give rise to fat emboli in distant foci Fat emboli have been found in these animals in the pulmonary capillaries in the heart and in the glomeruli of the kidney The fat emboli may result in damage to these structures One must remember however that a hemorrhagic nephritis is produced in animals on a choline deficient diet and this equally important pathologic process is independent of the fatty liver and is a collateral effect of the choline deficiency

Addition of choline to the diet results in the removal of fat from the liver In the early stages this occurs rapidly The delayed removal in the advanced stages is due to the difficulty in getting rid of the intercellular fat The intracellular fat is removed within a few days The extracellular fat remains unaffected for weeks or months Eventually the parenchymal cells appear to absorb the fat from the cysts for the cells become swollen with fat droplets while the fat cysts become smaller The parenchymal cells then dispose of this additional fat and the architecture is restored to normal However on occasions a fatty cyst may remain for many months as mute evidence of a once fatty liver The completeness of restoration of the liver is dependent upon the duration of the pathologic process as well as the degree of distortion of the liver architecture

Fatty Cirrhosis Dietary Cirrhosis

In 1937 and 1938 Connor expressed the view that fatty infiltration was a precursor of and resulted in hepatic cirrhosis Chaikoff with Connor and others produced cirrhosis preceded by fatty livers in normal dogs by feeding high fat diets We found in our experiments in guinea pigs and rabbits that animals which survived the fatty livers long enough developed cirrhosis and with the development of cirrhosis the fat content of the livers decreased From Best s description of the development of choline deficiency fatty liver and its restitution

with choline one may get the false impression that this process is always reversible and permanent cirrhosis does not follow It is g n erally agreed that dietary fatty livers eventuate in cirrhosis the point of contention among various observers is the site of origin of the fibrous tissue (periportal or centrolobular) and the mechanism of the development of fibrosis

The development of the large fatty cysts can readily result in compression of vascular channels and the resultant ischemia can lead to fibro is This view is upheld by a number of investigators (Himsworth Handler and Dubin Conner Hartford) Hartford gives a clear and concise description of the development of this lesion As was pointed out before the fat in choline deficient animals develop first around the central vein The large fat cysts compress not only the parenchymal cell but the sinusoids as well These large fat cysts are termed lipodiastaemata by Hartford The sinusoids in the centrolobular zone are compressed to the point where they can be delineated by their compressed endothelium and show no lumen at all These lipodiastaemata become encircled with fibrous tissue and it is invariable that the pressure of these large cysts coupled with the ischemia should result in the death of the parenchymal cells The lipodiastaemata eventually begin to lose the fat and decrease in size The route through which the fat leaves is unknown but this could occur by discharge into blood lymph or biliary channels Fibrous tissue proliferation increases as the lipodiastaemata atrophy Since the process begins and is furthest advanced around the central vein fibrosis arises at this point The centrolobular origin of the fibrous tissue is accepted by Hartford Gyorgy and Goldblatt Himsworth and Ashburn and coworkers Evidence and logic seems to support this view point This conclusion was difficult to arrive at especially since in the advanced process the trabeculae of fibrous tissue embrace increasingly larger areas and the architecture is so distorted that it is difficult to distinguish the relationships of the lobule to the portal canal



Fig 51 Cirrhotic li r in a r bb r prod ced by d etary mean (Fr m Spellberg and Keet n Am J M Sc 200 688 1940)

The (purely) mechanical theory described above has some valid objections We noticed a difference in response of guinea pigs to different types of fat butter fat producing marked fatty change while hydrogenated vegetable fat (Crisco) produced mild changes Gyorgy and Goldblatt (1943) also contend that the chemical nature of the fat is important Fats with a high content of unsaturated fatty acid as found in cod liver oil and also in lard increase necrosis by their destructive effect on tocopherol This leads us to the next problem namely dietary hepatic necrosis and the effect of other dietary deficiencies on the liver

Dietary Hepatic Necrosis

The elucidation of the mechanism of necrosis of hepatic cell is even of greater importance than the problem of fatty metamorphosis A fatty cell may maintain part or all of it function while a necrotic cell loses all its usefulness to the body economy In the last analysis death of a patient from liver failure is due to the loss of a majority of the functioning hepatic units and necrosis is responsible for much of this destructive process While as was noted above necrosis may follow marked fatty change we know from clinical experience that necrosis may be primary Therefore it is of

interest to review the experimental dietary approach to hepatic necrosis

The Role of Protein in Liver Injury

The realization of the importance of protein in maintenance of normal liver function is even of more recent date than the entire problem of nutrition in liver disease and is only about two decades old About 20 years ago some large clinics in this country prescribed a meat free diet to patients suffering from liver disease on the grounds that meat was toxic to the liver Some of the early observations on the possible relationship of protein metabolism to liver dis ease came from the clinic Attention was focused on proteins by the demonstration of low plasma proteins and especially albumin in patients with liver disease (Wiener and Wiener 1930 Foley Keeton and Kendrick 1935 Snell 1935)

It was pointed out above that the produc tion of fatty livers was dependent on a low protein diet which lacked lipotropic substances Deficiency of other essential amino acids also results in fatty livers

Sulfur Containing Amino Acids

Daft and coworkers in 1941 called attention to the importance of the sulfur containing amino acids by demonstrating that the hepatic cirrhosis produced in their animals on a pro tein deficient diet could be retarded by the administration of cystine In 1944 Himsworth and Glynn produced massive hepatic necrosis in rats on a diet containing 200 mg of casein a day If yeast was used as *the source of pro* tein the necrosis was more rapid and diffuse The difference between these two sources of protein appeared to be their content of methi onine When methionine was added in suffi cient amounts necrosis was prevented Since this lesion was not accompanied by fatty infil tration and choline did not influence it the importance of methionine independent of its lipotropic properties was established The methionine deficient diet resulted not c necrosis but post necrotic cirrhosis (no hyperplasia) if the animal survived *enough This cirrhosis differed from* portal cirrhosis and its experimental co

part the dietary cirrhosis produced by high fat and lipotropic factor deficient diet They termed the hepatic necrosis due to methionine deficiency trophopathic necrosis and that due to poisons such as carbon tetrachloride and chloroform toxipathic The possibility suggests itself that certain toxins such as cinchophen and trinitrotoluene may produce their effect by depriving the cells of essential amino acid and *therefore* cause a trophopathic type of necrosis

It was later shown by the use of purified amino acid supplements that cystine rather than methionine deficiency is responsible for this hepatic necrosis Since both are sulfur containing amino acids they have interchange able action in the body Methionine is con verted to cystine in the body and cystine has a methionine sparing effect (Rose and Wood Womack and Rose) For these reasons the confusion between these two amino acids oc curred Although cystine is the factor proven responsible for this type of necrosis (Glynn et al 1945) this fine differentiation is not impor tant clinically since methionine can act as a substitute for cystine

Another interesting observation in this form of hepatic necrosis is that if the sulfur contain ing amino acid deficiency is not marked the necrosis is confined chiefly to the left lobe of the liver which receives its portal blood supply from the colon and spleen while the right lobe which receives portal blood from the small intestine escapes injury This may be explained on the basis of the complete absorption of the *small amount of essential amino* acid by the upper small intestine and its delivery to the right lobe of the liver *while* the *left lobe of* the liver is completely deprived of it

Apparently bacterial infections or their toxins play a role in this type of hepatic necrosis Gyorgy pointed out that this type of nutritional hepatic necrosis cannot be produced in rats in a sterile environment The amelic dietary necrosis by sterilization of the estinal tract also suggests that bacteri r by products may play a role in and the discrepancy in ee right and left lobe of liv difference of the

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The role of tocopherol in the production of dietary necrosis due to sulfur containing amino acid deficiency will be discussed later (p ?9)

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It has also been noted that the environmental temperature influences hepatic necrosis due to deficiency of sulfur containing amino acids (Naftalen) The highest incidence of necrosis was at an environmental temperature of 70 to 74 F at lower temperatures 60 to 65 F and 35 to 50 F hepatic necrosis was reduced Pregnancy accelerates hepatic damage due to choline methionine and tocopherol deficiency (p 470)

The Pathogenesis of Sulfur Deficient Hepatic Necrosis

Circulatory factor The mechanism by which these amino acid deficiencies produce hepatic cell necrosis is postulated by Himsworth (1950) as being caused by circulatory impairment resulting from the swelling of the cell and compression of sinusoid This is supported by the observation that the water content of the necrotic liver is greatly increased (Abell et al 1950) and also by the observation that the necrosis is most marked in areas of extrinsic pressure on the liver as at the rib margin It seems highly improbable however that necrosis produced in such metabolically active organ as the liver by deprivation of a specific chemical substance should depend on such gross anatomical change as circulatory impairment One should look for a more subtle intracellular biochemical abnormality

Chemical factor Glutathione in the liver a sulfur containing substance vital in cellular metabolism is reduced in cystine deficiency (Leaf and Neuberger) as well as in poisoning by chlorinated hydrocarbons by selenium and in tocopherol deficiency All of these forms of liver injury may act by depriving the cells of their requirement of sulfur and disturbing the enzyme system in which glutathione is involved Increased cystine in diet may also have an untoward effect by disturbing the relationship between the reduced and oxidized form of glutathione (Himsworth 1950)

Protective Role of Proteins Against Poisons

In addition to the deleterious effects which result from depriving the liver of its protein or specific amino acid requirements it has been shown that protein has a protective effect on the liver against hepatotoxic agents such as carbon tetrachloride chloroform and arsenic This protective effect is superior to carbohydrates Fat has a deleterious effect on the liver and lowers its resistance to the noxious agents The method by which proteins protect the liver against these various poisons is not known but some subtle enzymatic process may be involved The deleterious effect of fat at least in the case of fat soluble poisons may depend on their greater solubility in this medium

The question as to what portion of the protein molecule affords the protection against the toxic agent remains unanswered A suggestion has been made by Neale that xanthin has a protective effect against chloroform intoxication While this has been denied by Ravdin and his coworkers it may have been a prophetic observation More recently in the studies on liver regeneration it was demonstrated that proteins afford the greatest stimulus for regeneration (Curd et al 1948 Newman et al Vars et al) Of the various proteins tried liver protein was found most effective and this apparently because of its high content of ribonucleic acid Nucleic acid has also been found

interest to review the experimental dietary approach to hepatic necrosis

The Role of Protein in Liver Injury

The realization of the importance of protein in maintenance of normal liver function is even of more recent date than the entire problem of nutrition in liver disease and is only about two decades old About 20 years ago some large clinics in this country prescribed a meat free diet to patients suffering from liver disease on the grounds that meat was toxic to the liver Some of the early observations on the possible relationship of protein metabolism to liver disease came from the clinic Attention was focused on proteins by the demonstration of low plasma proteins and especially albumin in patients with liver disease (Wiener and Wiener 1930 Foley Keeton and Kendrick 1935 Snell 1935)

It was pointed out above that the production of fatty livers was dependent on a low protein diet which lacked lipotropic substances Deficiency of other essential amino acids also results in fatty livers

Sulfur Containing Amino Acids

Daft and coworkers in 1941 called attention to the importance of the sulfur containing amino acid by demonstrating that the hepatic cirrhosis produced in their animals on a protein-deficient diet could be retarded by the administration of cystine In 1944 Himsworth and Glynn produced massive hepatic necrosis in rats on a diet containing 200 mg of casein a day If yeast was used as the source of protein the necrosis was more rapid and diffuse The difference between these two sources of protein appeared to be their content of methionine When methionine was added in sufficient amounts necrosis was prevented Since this lesion was not accompanied by fatty infiltration and choline did not influence it the importance of methionine independent of its lipotropic properties was established The methionine deficient diet resulted not only in necrosis but post necrotic cirrhosis (nodular hyperplasia) if the animal survived long enough This cirrhosis differed from human portal cirrhosis and its experimental counterpart the dietary cirrhosis produced by high fat and lipotropic factor deficient diet They termed the hepatic necrosis due to methionine deficiency trophopathic necrosis and that due to poisons such as carbon tetrachloride and chloroform toxipathic The possibility suggests itself that certain toxins such as cinchophen and trinitrotoluene may produce their effect by depriving the cells of essential amino acid and therefore cause a trophopathic type of necrosis

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to have a protective effect against carbon tetrachloride poisoning (Sundareson)

Strangely enough it has been shown that choline deficient (cirrhosis producing) diets do not impair the rat s ability to regenerate its liver after partial hepatectomy (Williams 1951) although the liver cells were heavily laden with fat This author concludes that in dietary cirrhosis the only alterations are in the vascular bed and reticulum framework and the number of parenchymatous cells are unchanged This is not in keeping with Hartford s description of the rupture of fat laden parenchymatous cells which could not act as a functioning unit Even in advanced cirrhosis evidence of regeneration is still present but this regeneration apparently cannot keep pace with necrosis Moreover even the regenerated cells may be incapable of carrying on normal function and therefore while anatomically present are physiologically ineffective

The Role of Vitamins in Hepatic Injury

Tocopherol

In 1940 Hamilton and Rich reported the production of dietary cirrhosis in rabbits which was prevented by the administration of alpha tocopherol We were unable to confirm this observation when we used casein as the source of protein It was mentioned that hepatic necrosis was produced more readily when an English brand of yeast was substituted for casein as the source of protein When the same experiments were repeated with an American yeast these results were not reproduced It later proved that this difference in action of the two types of yeast and the yeast as compared with the casein was due to the difference in tocopherol content of these substances Thus tocopherol deficiency has been found to be an important factor in dietary hepatic necrosis The other curious fact is that such divergent chemicals as tocopherol and methionine should have a similar effect on hepatic necrosis Thus an animal on a methionine (cystine) deficient diet may be protected by tocopherol or vice versa Tocopherol like methionine has been shown to have a protective effect against certain hepatotoxic agents (CCl_4 Hove 1948) Such identical action of two chemically divergent substances may be explained on their similar action on the intracellular enzymatic process especially the one connected with the sulfhydryl group Some of the analogues of tocopherol have been found to be quite inert in this respect (Selzer et al 1951) Experimentally induced hepatomas in mice accumulate dietary tocopherol more rapidly than the normal liver cells and the tumor cells retain the vitamin tenaciously during depletion Tocopherol had a variable effect on the incidence of these tumors

While this type of hepatic necrosis has been found by most investigators to be devoid of fatty infiltration Abell and Beveridge (1951) found some increase in lipids in the prenecrotic period and choline partially prevented this fatty infiltration This observation points up the fact that even experimental dietary liver damage is not a pure deficiency but one that involves several factors This must be remembered particularly when dealing with clinical problems in which deficiencies are never single but involve groups of substances This is compounded by the fact that both the lipotropic factors and the factors responsible for preventing hepatic necrosis reside in the protein portion of the diet

B Complex

Fatty degeneration and focal necrosis has been produced in the rat by diets deficient in the B complex but supplemented by thiamine riboflavin and panthothinic acid Protection was afforded by including a source of the entire B complex (Gyorgy and Goldblatt 1939) It was assumed that the liver injury was due to the lack of one of the then unknown factors in the B complex

Liver extract has been used for many years empirically in the treatment of liver disease Recent experimental observations point to some rationale for its use The superior value of liver protein mentioned above suggests that it contains some factor essential for liver cell physiology It has also been shown that liver extract has a lipotropic effect equal to choline and this effect is due to some unknown lipotropic substance (Drill and Hall 1950)

Vitamin B_{12}

This "unknown" lipotropic factor in liver extract may actually be its active hemopoetic fraction B_{12}. Drill and McCormick (1949) showed that small doses of B_{12} had a marked lipotropic effect in animals on high fat low protein diet, and this effect was not due to the small amounts of choline contained in it. The lipotropic effect of B_{12} in large doses was confirmed by Gyorgy (1950). B_{12} was also shown to have a protective effect against CCl_4 poisoning (Koch Weser et al, Mushett 1950). The Chicago group thought that this protective effect of B_{12} in carbon tetrachloride intoxication was due to a vasodilating effect. Regardless of the exact mode of action, it seems established that B_{12} among its many other functions has an important role in liver metabolism.

Folic Acid

Folic acid seems to act synergistically with B_{12} and augments the lipotropic effect of the latter substance. B_{12} itself may have a choline sparing effect combined with folic acid; it may make the inclusion of the labile methyl group in the diet unnecessary. Stekol and coworkers (1950) achieved a lipotropic effect with a labile methyl (CH_3) free diet supplemented with folic acid, B_{12} and homocystine. Bennett and her coworkers observed normal growth of rats on similarly supplemented diets. The effectiveness of liver extract may therefore depend, at least in part, on its content of B_{12} and folic acid.

Biotin

In the study of biological phenomena, observations sometimes are made which seem to indicate that nature is working at cross purposes. These paradoxical activities are paradoxical only because we assume on teleological ground that there is a "purpose" in all the laws of nature. Thus, the bacteria in the gastrointestinal tract may play a role in the production of nutritional liver necrosis and yet these same bacteria synthesize fractions of the B complex and vitamin K essential for liver physiology. It was pointed out before that thiamine and biotin may stimulate the production of certain types of fatty livers.

Sterilization of the intestine of rats on a basal diet by means of sulfaguanidine resulted in degenerative and necrotic lesions in the liver. These lesions were preventable by liver or a combination of folic acid plus biotin (Gross et al.). Thus, biotin may be essential for normal liver physiology. Sterilization of the gut may have a salutory effect on one side of the ledger and a deleterious effect on the other.

Carbohydrates

The protective effect of carbohydrates against hepatotoxic agents were among the earliest observations dealing with the importance of the food stuffs in the economy of the liver. The protective action of carbohydrates against chloroform poisoning was reported by Whipple and Sperry in 1909 and against chloroform and phosphorous by Opie and Alford in 1915. While the more recent observations by Messinger and Hawkins, Miller and Whipple, Goldschmidt and coworkers assign greater protective action to protein, carbohydrates are admittedly protective. Soskin disputes the claims for the greater protective action of proteins and cites experimental evidence from his laboratory that if the protein is adequate, a high carbohydrate intake results in the longest survival of animals exposed to carbon tetrachloride.

It has been assumed that carbohydrate protects the liver cells by virtue of glycogen deposition. This is disputed by the observations of Goldschmidt and coworkers who observed poor resistance of glycogen laden cells to chloroform poisoning. Others have observed abundant glycogen cells of a liver that is the seat of extensive necrosis.

Bollman in a recent (1949) appraisal of this problem was unable to find satisfactory evidence that the amount of carbohydrate in the diet or the amount of glycogen in the liver cells influenced directly the liver's resistance to noxious agents. The importance of carbohydrates in the diet may depend on its conservation of proteins. However, from many clinical as well as laboratory observations, it seems obvious that administration of glucose intravenously has a favorable effect on the injured liver.

Bollman also points out that after prolonged (three months) common duct obstruction in dogs feeding of a predominantly carbohydrate diet may succeed in maintaining the animal for many months while a diet entirely of meat results in its death within a week The objectionable feature of the meat diet may be the meat extractives and not the proteins (p 286) Some deleterious effects on the liver have also been noted in dogs given large amounts of glucose by continuous intravenous drip Jaundice and degenerative changes in the liver appeared while the cells were over filled with glycogen

Clinical Implications

The array of evidence presented above leaves little doubt of the important role dietary constituents play in experimental liver injury Since there may be a difference in response in different species one cannot unqualifiedly assume that this is applicable to man While there may be differences in particulars it is nevertheless a fair assumption from the laboratory data that the human liver is vulnerable to dietary deficiencies This assumption seems reasonable since many species of animals (dog rat mouse guinea pig and rabbit) showed a similar response to dietary manipulations It would be odd indeed that man should be an exception We know from other investigations that when several species respond in like manner to a given experimental situation man reacts similarly This is especially true of problems dealing with diet and dietary deficiencies Most of our knowledge about vitamins and human nutrition stems from animal experiments

The difference that one should expect in man is not one due to species but rather to the complexity of the human diet and the multiplicity of the deficiencies Unlike the laboratory animal which can be maintained on purified amino acids our diet consists of complex proteins which may show infinite variations from day to day When a deficiency occurs it usually includes a group of vitamins and proteins in general Moreover the proteins are the seat of the lipotropic factor as well as the essential amino acids Also deficiencies may be periodic and modified by other diseases and various toxic agents For these reasons one would hardly expect to see in man such pure and clear cut nutritional liver injury as has been abundantly demonstrated in laboratory animals

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Diet and Liver Disease in Man

Correlation in North America and Europe

In parts of the world such as the United States where the general economic level of the population permits an adequate diet serious dietary deviations are usually based on personal factors and require a careful history for elucidation Dietary histories are notoriously inaccurate unless the diet is so grossly inadequate that delving into details is not essential for evaluation Patients are notoriously lax in answering questions about their diet the questioner can readily influence the answers and it is very difficult to quantitate the answers when obtained Thus it is nearly impossible to obtain an accurate idea from patients about amount and character of proteins or quantity of fat consumed except in the vaguest terms The rare exceptions are dietary faddists who subsist on one or two articles of food or persons on restricted diets imposed for

herapeutic purposes For this reason little elp can be obtained from clinics or private ractice to test the hypothesis of the relation nip of diet to liver disease in man

Gross dietary abnormalities are present in wo large groups of individuals the analysis of which may shed some light on this problem These groups are alcoholics or victims of war That liver injury is significantly more frequent among chronic alcoholics than in the general population is unquestionably true (p 396) Voegtlin and coworkers found some liver dys unction in all but 9 6% of a group of 300 chronic alcoholics The alcohol per se is not the sole responsible factor but the neglect of diet is probably the important factor for the ollowing reasons

1 Large quantities of alcohol in animals to the point of continuous intoxication does not produce cirrhosis but a mildly fatty liver and even this slight abnormality can be prevented by enforcing an adequate protein intake In acute experiments in rats fatty livers were produced by means of alcohol and the main tenance of a high protein diet however the animals became comatose and did not eat for periods of time Chaikoff and his associates (1948) tried to differentiate between the effect of alcohol and concomitant dietary deficiency in liver injury in animals but they were unable to obtain clear cut conclusion There is no good experimental proof that liver damage from alcohol can be dissociated from malnutri tion

2 Many of us have had experience with chronic alcoholics of many year duration who show normal livers from a functional and ana tomical stand point

3 Total abstainers and even children e pe cially in countries where malnutrition is com mon suffer from chronic liver disease

Alcoholics who drink steadily and per ist ently are more likely to develop erious liver injury than tho e that drink sporadically Presumably in the latter group an adequate diet in the interim allow for complete recovery According to Voegtlin and coworkers the two finding mo t likely to accompany hepatic dys function in alcoholics are obesity and evidence of vitamin deficiency Both of these features are signs of malnutrition The obesity suggests a high caloric intake but does not assure a proper balance of all dietary es entials Nutri tional diseases are most likely to appear not in starvation (low total caloric intake) but in normal caloric intake with deficiencies in essential elements Other evidence of vitamin deficiency of course further confirms the die tary abnormality Chalmers and coworkers found hi tologic abnormalitie of the liver in chronic alcoholics and this was correlated with abnormal diets during the alcoholic sprees and there was rapid improvement after treatment with an adequate diet Romano studied the diet in a group of alcoholics and found it gro sly inadequate in 79% In general it may be concluded that while alcohol per se may have a deleterious influence on the liver this has not been proven but dietary abnor malities are abundant in alcoholics and the alcohol then may act as a synergistic factor

Repatriated prisoners of war from the Pacific Theatre where the diet was abnormal in quality rather than quantity studied by Meienberg and Snell showed abnormal liver function tests in about half of those tested Two of 50 young men studied developed cir rhosis in the ab ence of any other etiologic agent except malnutrition During the epi demics of hepatitis experienced in the American Army the mortality wa much lower in 194 than in 1944 and 1945 Thi difference may be attributed to the inferior combat rations in the latter period

Occasionally one encounter apparent excep-tions to thi idea of the deleterious effect of malnutrition on liver disea e Two such cases are referred to on page 70

Correlation in Africa and Asia

The implication of deficient diet in the pathogene i of fatty and cirrhotic liver in natives of Africa and Asia i more direct and convincing Correlation of the deficient diets of the Bantu tribes of Africa with their high incidence of cirrhosis and carcinoma of the liver has been mentioned (Chapter 18) Their diet consi ting of maize and sour milk when fed to experimental animals resulted in hepatic injury The Gillmans have demon trated

markedly fatty livers and the eventual development of cirrhosis and hemosiderosis in malnourished natives The etiologic role of the diet cannot be doubted

The high incidence of cirrhosis especially among children in certain provinces of India is likewise inextricably associated with dietary deficiencies While it is true that the high incidence of helminthic and other infections especially malaria (Chapters 32, 33) have a bearing on this problem the miserable diet is probably of foremost importance Alcohol cannot be implicated in most of these groups either because of age or because of abstinence for religious reasons A 9 3% incidence of *cirrhosis was found in a group of over 500* autopsies in a province in India (Vizagapatam) where alcohol is not used (Tirumurti 1934)

The study of Fernando and coworkers from *Ceylon is noteworthy The death rate from* cirrhosis in Colombo is 13 6 per 100 000 population almost triple that of England and Wales (4 7 100 000) Of the 102 cases of cirrhosis studied one native group contributed a disproportional number of cases This group consisted mainly of vegetarians The poorer nutritional quality of vegetable as compared with animal proteins is well known Vegetable proteins are especially poor in lipotropic factors 85% of the entire group had portal cirrhosis In 48 8% of 43 patients in whom reliable dietary history was obtained malnutrition appeared to be the cause of the cirrhosis Fatty infiltration of the liver was a prominent histologic feature and this was apparently due to deficiency in the lipotropic factors In 27 9% alcoholic consumption was excessive and was considered important in the pathogenesis of the cirrhosis

It has been suggested by several observers that the diet in the various groups with a high incidence of cirrhosis may be deficient in other specific nutrient factors which have been shown experimentally to be implicated in hepatic injury Selzer and coworkers pointed out that maize and soured milk which forms he bulk of the diet of African natives with a ery high incidence of cirrhosis is deficient in alpha tocopherol The gamma tocopherol found in this food (Hove and Hove) does not have the same protective action on the liver as the alpha form Protein deficient diets and proteins predominantly of vegetable origin may be deficient in B_1 which is also important especially in the presence of deficiency of labile methyl group

Summary

The preponderance of evidence presented above both experimental and clinical implicates dietary deficiency as the factor responsible for liver injury the production of fatty livers and cirrhosis No one doubts the importance of diet in liver physiology and pathology but there remain questions and disagreements *about particular details*

The exact place of alcohol in the pathogenesis of cirrhosis is still not completely settled Dietary deficiency seems to play the major role and *in many cases the sole role in* pathogenesis However alcohol may contribute to the development of a fatty liver either primarily or secondarily by interfering with the utilization and/or absorption of some of the food substances ingested

Another unsettled problem is the relationship of fatty metamorphosis to cirrhosis in man Doubt has been expressed that the fatty liver is a precursor of human cirrhosis (Dible) and that the fatty changes are per se (experimental and clinical) responsible for the ensuing fibrosis Dible bases his doubts on the relative infrequency of increased fat in a group of 69 cirrhotic livers and on the theoretically long period of time that this transformation would require Less than half of these livers had an excessive amount of fat although some of these were early cirrhosis according to other criteria He estimates that the 100–300 days that is required in the rat for the change from a fatty liver to cirrhosis is equivalent to 7– 0 years in man

It is true that fatty livers of that duration are not a frequent occurrence and yet with more widespread use of needle biopsy technique the duration of fatty livers may be found to be surprisingly long It does not necessarily follow that the time of the development of cirrhosis in man must parallel that in the rat That fatty infiltration is not a neces

sary precursor of toxic or post necrotic cirrhosis is admitted by all

Another difference between nutritional (fatty) cirrhosis in animals and portal cirrhosis in man is that in the former the fibrosis begins in the center of the lobule while in the latter it is periportal in origin

In nutritional, alcoholic or portal cirrhosis there is so much accumulated clinical evidence that the fatty liver is a frequent but not an invariable precursor of this type of cirrhosis that we are not justified in discarding it The large soft (fatty) liver is a common finding of the early alcoholic while the small atrophic fibrotic liver is a feature of advanced cirrhosis Case reports have appeared in the literature demonstrating by means of needle biopsy the disappearance of fat and the increased prominence of fibrous tissue (Davis and Culpepper) observations duplicated in my own experience (p 305 Fig 58)

Ceroid in Experimental and Clinical Cirrhosis

In 194 Gyorgy and Goldblatt observed in unstained sections of livers of rats with dietary cirrhosis light greenish yellow globules enmeshed in the periportal fibrous tissue This substance was later called ceroid by Lillie and coworkers This is a hyaline fluorescent substance which is basophilic and acid fast takes on lipid stains but is insoluble in lipid solvents It is probably a lipoprotein derived from the intracellular fat Its development is enhanced by administration of cystine and prevented by choline (Popper et al) and markedly reduced by tocopherol (Hartford) This substance is probably related to certain types of unsaturated fats and cod liver oil has also been implicated A similar substance has been found in rats receiving injections of cod liver oil and linseed oil According to Hartford red cells may so alter the characteristics of hepatic cell lipids as to transform them into a ceroid like substance and the deposition of ceroid interferes with hemosiderin deposition Ceroid may be found in other organs where it is brought by circulating macrophages which have transported it from the liver

The absence of ceroid in the human cirrhotic liver has been used by some as evidence that portal cirrhosis in man is not analogous to the disease in experimental animals Two other explanations have been offered which are more plausible 1 cod liver oil which is the most effective fat in the production of ceroid is not consumed by the human cirrhotic and 2 the diet of patients with cirrhosis may not be deficient in tocopherol which inhibits ceroid formation Finally it should be mentioned that fluorescent substances resembling ceroid have been observed in human cirrhosis

Kwashiorkor

Synonyms

Malignant malnutrition starch and flour dystrophy mehlnahrschaden

Definition

Kwashiorkor is a nutritional disease confined chiefly to infants and children of the tropics characterized clinically by a peculiar dermatitis depigmentation of hair diarrhea emotional changes edema and ascites and pathologically by fatty and cirrhotic liver and atrophy of pancreas

Introduction

This disease is of extreme interest since it forms an important link between much of the recent experimental work in nutritional liver injury and a disease in man With some minor exceptions it is the human counterpart of the fatty liver in the depancreatized dog and the nutritional cirrhosis in the rat It is indeed a sorry comment on our civilization that vast numbers of children become trapped in a state of malnutrition as inexorable as that inflicted on our experimental animals Those who are interested in this expansive human experiment should read the excellent account of Davies in the 7th Conference on Liver Injury as well as the other publications of Davies and Trowell

Etiology

Geographic distribution While it is seen chiefly in East Africa it is found all over the tropics and with some modifications has been encountered all over Africa in Central and South America India Indochina and Indo

nesia But given the proper nutritional state it may occur anywhere since a similar lesion was described by Veghelyi during the siege of Budapest Kark has seen a Negro child at Cook County Hospital in Chicago who had the clinical features of this disease

Age and sex The acute disease occurs chiefly in children between 1 and 4 years of age, but the more chronic form occurs in older children and young adults Males are slightly more commonly affected than females

Pathogenesis

Inadequate diet is unquestionably responsible for this widespread disease Children in these tropical countries are weaned late Some are not weaned until the age of five or six While they subsist on mother s milk the process is held in abeyance When the child is weaned he is switched from the mildly deficient protein diet of mother s milk to a diet composed almo t exclusively of carbohydrate little fat and a negligible amount of protein This results in an exhaustion of the enzyme secreting cells of the pancreas small intestine and salivary glands These glands are unable to synthesize enzyme because of lack of protein and they eventually atrophy The atrophy of the pancreas and intestinal glands causes a further loss of proteins and fat from the bowel with further malnutrition and the development of a fatty liver The fatty liver is thus a consequence of a physiological pancreatectomy The islet cells are not involved and diabetes does not develop The fatty liver eventually changes into cirrhosis Parasites play no part in the pathogenesis of this disease

Pathology

The primary and most important pathology in this disease is found in the liver and pancreas

Liver The morphological alterations in the liver vary with the age of the patient or rather with the age or duration of the disease Thus under five years of age the liver is enlarged pale yellow in color soft or only slightly firmer than normal greasy and the sections float in the fixing fluid Microscopically there is a tremendous amount of fat accumulation so that in the advanced stage it is difficult to identify the tissue as liver The accumulation of fat begins at the periphery where the fat is always present in greater abundance but eventually the entire lobule is involved This is the reverse of the central accumulation of fat in experimental fatty liver in animals The fat distended cells compress the sinusoids at the periphery of the lobule and in the portal areas lymphocytes some polymorphonuclear leucocytes and eosinophiles appear Reduplication of reticulum fibers takes place in the periphery of the lobule and in the periportal spaces This eventually leads to fibrous hyperplasia which surrounds the periphery of the lobule and eventually penetrates into the lobule

In older children 5 to 10 years and 10 to 0 years of age the process in the liver shows mor advan ed fibrosis and cirrhosis but at the same time a marked decrease in fat Thus this process seems to follow the same steps as the nutritional cirrhosis in animals with fatty liver antedating the full blown cirrhosis The liver is now grayish in color smaller and cuts with resistance The surface is granular or shows fine uniform nodularity resembling portal or monolobular cirrhosis Some livers however resemble postnecrotic cirrhosis with gross scarring and large nodules

Microscopically it is interesting to note the reciprocal relationship between fibrosis and fat accumulation The greater amount of fibrosis and smaller amount of fat is seen in the older children The fibrosis may be quite marked and thick bands surround individual lobules (monolobular) so that the lobular architecture is still distinct However in most cases larger areas of necrosis with superimposed regenerating nodules result in gross distortion of the architecture resembling more portal or post necrotic cirrhosis These further changes are seen in the most advanced cases With the loss of fat and increased fibrosis there is also increased cellular infiltration

Adult immigrants to Uganda may develop the acute form of the disease and show preponderantly fatty changes (because of its recent origin) as seen in infants however in these adults there is usually more fibrosis and cellular infiltration The increased fibrosis suggests the presence of preexisting hepatic damage Iron pigment deposition is not a conspicuous feature in the liver of the Uganda natives but is marked in the Bantu (Gillman) The higher concentration of iron in the diet of the Bantu may account for the hemosiderosis Hemosiderosis of the liver has been observed in cases of starvation from German concentration camps (Chapt r 73)

Pancreas The chief gross feature in the pancreas is a marked state of atrophy Microscopically there is first atrophy of enzyme secreting cells with complete disappearance of zymogen granules Finally these cells are reduced to a nucleus with a thin rim of cytoplasm around it The atrophy does not involve the ductal epithelium the islet cells or the blood vessels It has been suggested that the islet cells may actually hypertrophy Later there is an increase of fibrous tissue and the organ becomes

sclerotic. Some have suggested that cystic dilatation simulating cystic fibrosis of pancreas occurs in this disease (Gillman, Gilbert & Gillman) but Davies denies any such similarity. The *parotid gland* and other salivary glands may show a similar atrophic process.

Other organs. Among the other organs involved, the kidney lesion is most interesting. The combination of renal and hepatic lesions is noteworthy in itself but the renal lesion is important because of its possible relation to the marked edema seen in this disease. The renal lesion has been referred to as proliferative glomerulitis by Hennessey, the most conspicuous feature of which is glomerular hyalinization. This hyalinization appears to start at the base of the glomerular tuft rather than at the center. There is a difference of opinion as to whether the apparent hyperplasia in the capsular epithelium is a true hyperplasia or a change in the character of the epithelium from a flat to a cuboidal type. Pericapsular fibrosis is also common. Since these renal lesions resemble that seen in portal cirrhosis one may speculate that they result from the liver injury.

Intercurrent infections are a frequent cause of death in these patients and pneumonia is especially a common finding. Tuberculosis is another infection commonly encountered. The spleen may be enlarged and is quite normal but this may be due to malaria and other infections. Esophageal varices are practically never encountered. Dilated small intestine showing atrophy of mucosa is a frequent finding. Carcinoma of the liver is one of the most common malignancies in adults. Davies has also noticed cardiac lesions which may be associated with Kwashiorkor and calls it endomyocardial necrosis. The lesion consists of subendocardial hydropic degeneration of myocardium resembling beriberi but in response to thiamine chloride. Eventually the involved muscle fibers break up and disintegrate to be replaced by scar tissue. These patches of fibrosis especially in the left ventricle may have mural thrombi adhering to them. It is thought that vitamin E deficiency may play a role in the production of these lesions.

Clinical Features

In the typical case the beginning in infancy there is normal development for the first six months. It appears that the mother's diet which is deficient in protein is adequate for the first six months. Since breast feeding is commonly continued for several years, failure in growth, depigmentation of skin and hair and lethargy begin to appear after six months. The symptoms become more marked when the child is completely removed from the breast and placed on the adult diet which is high in carbohydrate but markedly deficient in protein. This diet consists chiefly of cereal gruels and cooked banana.

Because the disease becomes acute when the child is weaned it was supposed that the disease was due to maternal rejection. However, the abrupt and drastic decrease in the protein content of the diet is more potent than the hypothetical psychological insult.

The change in the personality and disposition of these children is remarkable and is due to biochemical rather than psychological defect. They become irritable, listless, uninterested in their environment, refuse to play and lie curled up for hours. These changes in personality in the important formative years are most important since even if the child recovers, mental retardation and the negative personality may persist.

Diarrhea is another important symptom and may signal the onset of the disease. The symptoms may be intermittent. The stools are bulky, frothy and fatty resembling the stool of sprue or celiac disease. Much undigested material can be seen in these stools on gross inspection. Diarrhea becomes persistent and severe in the fatal cases. The patient becomes intolerant to carbohydrate which increases the diarrhea.

Anorexia is also a symptom which becomes severe but vomiting is rare. Increased salivation has been noted. The tongue is furred in some and smooth and denuded in others.

The change in color, texture and character of hair is conspicuous. The kinked black hair of the African child becomes brown, red or even blonde and straight and soft, hence the name Kwashiorkor meaning "red boy." The dermatitis begins to peel especially in the flexures and ulceration and infection follow. The skin areas involved show marked increase of pigment with generalized hyperpigmentation. The rash unlike that in pellagra is not confined to exposed areas. It almost always begins in the inguinal region and the axillae are involved. Areas of pressure such as buttocks are commonly involved.

While growth is stunted there is no apparent loss of weight or marasmic appearance. Subcutaneous fat may actually be increased on

nesia But given the proper nutritional state it may occur anywhere since a similar lesion was described by Veghelyi during the siege of Budapest Kark has seen a Negro child at Cook County Hospital in Chicago who had the clinical features of this disease

Age and sex The acute disease occurs chiefly in children between 1 and 4 years of age but the more chronic form occurs in older children and young adults Males are slightly more commonly affected than females

Pathogenesis

Inadequate diet is unquestionably responsible for this widespread disease Children in these tropical countries are weaned late Some are not weaned until the age of five or six While they subsist on mother s milk the process is held in abeyance When the child is weaned *he is switched from the mildly deficient protein diet of mother s milk* to a diet composed almost exclusively of carbohydrate little fat and a negligible amount of protein This results in an exhaustion of the enzyme secreting cells of the pancreas small intestine and salivary glands These glands are unable to synthesize enzymes because of lack of protein and they eventually atrophy The atrophy of the pancreas and intestinal glands causes a further loss of proteins and fat from the bowel with further malnutrition and the development of a fatty liver The fatty liver is thus a consequence of a physiolog cal pancreatectomy The islet cells are not involved and diabetes does not develop The fatty liver eventually changes into cirrhosis Parasites play no part in the pathogenesis of this disease

Pathology

The primary and most important pathology n th s d sease is found in the l ver and pancreas

Liver The morpholog cal alterat ons in the l ver vary w th the age of the pat ent or rather with the age or durat on of the d sease Thus under five years of age the liver is enlarged pale yellow in color soft or only sl ghtly firmer than normal greasy and the sect ons float in the fixing flu d M croscop cally there is a tremendous amount of fat accumulat on so that n the advanced stage it s d fficult to dent fy the t ss e as l ver The accumulat on of fat beg ns at the per phery where the fat s always present n greater abundance but eventually the ent re lobule is involved Th s is the reverse of the central accumulat on of fat in experimental fatty l ver n animals The fat d stended cells compress the s nuso ds at the periphery of the lobule and in the portal areas lymphocytes some polymorphonuclear leucocytes and eos noph les appear Redupl cat on of reticulum fibers takes place in the periphery of the lobule and in the per portal spaces Th s eventually leads to fil rous hyperplas a wh ch surrounds the periphery of the lobule and eventually penetrates into the lobule

In older ch ldren 5 to 10 years and 10 to 0 years of age the process in the liver shows more advanced fibros s and c rrhos s but at the same t me a marked decrease in fat Thus th s process seems to follow the same steps as the nutrit onal cirrhos s n an ma s with fatty liver antedating the full blown c rrhos s The l ver is now grayish in color smaller and cuts with res stance The surface is granular or shows fine uniform nodularity resembl ng portal or mono lobular cirrhos s Some l vers however resemble postnecrot c c rrhos s w th gross scarr ng and large nodules

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the trunk and the typical pot belly develops *Edema* may further deceive the casual observer that loss of weight has occurred The edema may involve only the hands legs and face or become generalized It may be mild or very severe Other evidence of malnutrition such as cheilosis and sores at other mucocutaneous junctions are noted Photophobia is frequently present

The liver of course is enlarged but may be difficult to palpate because of the edema and intestinal distention The *spleen* may also be enlarged but this may depend on concurrent disease such as malaria

Ascites of a massive degree is frequently found but dilated periumbilical veins and bleeding esophageal varices are rarely seen It is curious that in spite of development of advanced cirrhosis evidence of portal hypertension is rarely seen The explanation of this phenomenon is not at hand although the problem is of fundamental importance

Fever low grade may be present even in the uncomplicated disease Since superimposed infection especially pneumonia commonly complicates the picture high fever may be due to this

Chronic Disease in Adults

The more chronic disease in the young adult shows milder symptoms The apparently healthy African adult shows less stamina than his European brother Feminization of the African male is thought to be due to decreased destruction of estrogen by the impaired liver Gynecomastia has been observed in 3 to 5% of African workers and may be on this basis Skin lesions mucous membrane lesions and salivary gland changes are seen which are thought to be due to nutritional deficiency Scarring of the pancreas and liver at autopsy of African natives dying from other causes is indicative of the residuals of the infantile disease For this reason the apparently normal African adult has a very low resistance to hepatotoxic agents and steatorrhea and creatorrhea is easily provoked

Laboratory Findings

Anemia of a macrocytic hypochromic variety is frequently encountered This does not depend upon malaria or sickle cell anemia The leucocyte count is normal unless there is an intercurrent infection

Serum proteins are decreased but the decrease is in the albumin fraction so that there is a reversal of the albumin/globulin ratio Liver function tests are abnormal and the degree of abnormality depends on the severity of the hepatic lesion

Pancreatic enzyme studies of blood and of duodenal intubation should show decreased levels from both sources

Stools reveal an increased fat content Trowell found a stool fat content in some of his cases between 33 and 57% The fat is both in the form of unsplit fat and fatty acids indicative of both a lack of pancreatic lipase and defective intestinal absorption Increased nitrogen excretion occurs if the protein intake is increased

Blood Sugar In spite of the extensive pancreatic involvement the blood sugar is normal An oral glucose tolerance may reveal a flat type of curve similar to the one seen in sprue and probably also depends upon the poor absorption by the atrophic mucosa

X ray of the small bowel shows abnormal mucosal pattern disturbed motility areas of dilatation and spasm moulage formation and segmentation in general a pattern considered characteristic of sprue

Prognosis

That the prognosis of the untreated disease is grave is seen by the staggering infant mortality in the areas where this disease is common It has been estimated that in Uganda 75% of infants between the ages of six months and three years are affected by the syndrome (Trowell and Muwazi) It is equally true that many of the milder cases survive to adulthood but with evidence of impaired hepatic and pancreatic function and scars in these organs at autopsy

Treatment

Vitamins The administration of vitamin alone is of no avail and may even be deleterious A superimposed vitamin deficiency may be present and differs in different localities Even in South Africa where the disease has

been considered as infantile pellagra (Gillman) the administration of nicotinic acid may alleviate some of the symptoms such as the skin lesions but the patient dies promptly

Lipotropic agents Lipotropic agents including choline have been tried but did not produce the desired results In this respect the disease differs from the disease in depancreatized dogs or rats on a choline-deficient diet

High protein diet Administration of a high protein diet results in a rapid amelioration of symptoms Before the patient begins to improve there is a swelling of the parotid gland and apparently a swelling of the pancreas The enzyme secreting cells in these glands recover and begin to produce the digestive enzymes The stools improve the steatorrhea stops and the entire clinical picture becomes reversed *The final outcome depends on the severity of* the disease its duration and presence of intercurrent infection If irreparable damage has not been done to the pancreas a high protein diet should produce a cure Davies has demonstrated that during high protein therapy there is rapid mobilization of fat from the liver and the sinusoids are filled with lymphocytes which apparently function in the removal of fat from the liver It will be recalled that Hartford postulates other avenues of removal of fat from the liver of animals treated with lipotropic agents (p 98) Dean demonstrated that these patients respond well to milk proteins but are intolerant to carbohydrates which produce diarrhea

Powdered stomach The Gillmans found that 10 gm a day of powdered stomach (Ventriculin—Parke Davis) administered orally had a remarkable effect on the fatty liver and resulted in rapid diuresis This occurred after an apparently refractory period of feeding raw pancreas These workers postulate some subtle interrelationship between stomach liver and kidney which is responsible for the edema and other manifestations of the disease The powdered stomach supposedly supplies a missing factor which restores a normal physiologic state

Differential Diagnosis

In the differential diagnosis one has to consider other diseases producing steatorrhea namely sprue celiac disease and pancreatic steatorrhea In a sense Kwashiorkor is a form of pancreatic steatorrhea but it differs in pathogenesis The diagnosis of this entity depends on finding the steatorrhea associated with severe malnutrition in tropical localities or in disaster areas involving a large segment of population and especially children The skin lesions are a distinguishing feature along with small bowel and pancreatic involvement *and fatty liver or cirrhosis Sprue and celiac* disease are primarily due to small bowel involvement while in pancreatic steatorrhea the pancreas alone is involved and there is no history of malnutrition

Differentiation of Kwashiorkor from pellagra may become a matter of semantics according to some since this disease has been referred to as infantile pellagra But the evidence favors this being a distinct disease The skin lesion in pellagra is confined to or more severe in the areas exposed to sunlight This is not true in Kwashiorkor The fatty diarrhea is not a feature of pellagra Finally nicotinic acid will produce a complete remission of symptoms in pellagra but it will not in Kwashiorkor

Enteric infection such as dysenteries and typhoid fever may have to be considered but the febrile nature of these illnesses should lead to bacteriological identification Tuberculosis can be ruled out by demonstrating the pulmonary involvement Nephritis may be confusing but the urinary finding should clarify the problem

42—Fatty Liver—Hepatosteatosis

The fatty liver is of interest to the clinician not only because of its relation to experimental liver injury and as a stage in the pathogenesis of or its association with portal cirrhosis but as a clinical entity in itself One finds not infrequently at postmortem or in the present era with needle biopsy fatty metamorphosis of varying degree as the only histologic abnormality in the liver

Mechanisms of Production

Four possible mechanisms may be enumerated by which the liver or for that matter any other organ can become fatty the liver however because of its strategic position in the metabolism of the foodstuffs is more vulnerable to this change than other organs These mechanisms are

1. Abnormal amount of fat delivered to the liver
2. Interference with transport of fat away from the liver
3. Decreased utilization of fat by the liver and
4. *Increased synthesis of fat by the liver*

It can be readily seen that these various mechanisms are *interrelated and interdependent* the final result depending upon an equilibrium between these four mechanisms which operate normally When the scale becomes tipped in one direction abnormal accumulation of fat result

Abnormal amounts of fat may be brought to the liver from two sources (1) from the fat depots or (2) from the ingested food But actually if the transport of fat from the liver were *highly efficient no excessive deposition of fat would occur* Thus we see that the first two mechanisms transportation to and away have a reciprocal relationship and fatty liver can occur because of a disturbance of this *normal* equilibrium To these two can be added a third mechanism For the disposal of fat by the liver depends not only on its transportation *away but its utilization by the liver so that,* if the utilization could be stepped up when more fat is brought to the liver the lipids could be maintained at a normal level conversely if utilization falls markedly liver fat *accumulates even when delivery is normal* Finally the liver which can synthesize fatty acids from acetate may increase its production of this foodstuff and in the face of unaccelerated utilization or removal of fat increase of *its lipid content will occur (Fig 56)*

Cause of Fatty Liver

The immediate cause of fatty liver is any factor or group of factors which disturb this *equilibrium These factors are numerous but* because of the concerted investigation of the role of diet and because of its clinical importance we are apt to forget that diet is only one of the various etiologic factors The immediate *causes of fatty livers may be classified* as follows

- I Dietary
  - A High fat diet
  - B Over feeding?
  - C *Low protein diet*
  - D Diet deficient in lipotropic factors
  - E Deficiency in certain vitamins
  - F Under feeding (starvation)
  - G Pancreatic disease
- II Toxins
  - A *Carbon tetrachloride*
  - B Phosphorous
  - C Chloroform etc (See Section V)
  - D Alcohol?
- III Anoxia
- IV Infections
- V Endocrine
  - A Diabetes
  - B Anterior pituitary hyperfunction

Classifications are useful to clarify certain aspects of a problem in order to help the mind

to retain them however they should not be regarded as rigid fence separating the various compartments but as tributaries of a river which are interconnected fluid and changing Thus the various subgroups of this classification as is the case with many others are interrelated and have a bearing on each other Some of these points have been alluded to in the section dealing with the experimental phase of the problem and elsewhere but it may be worth while to bring these together briefly

Dietary abnormalities are probably the commonest cause of the production of clinical fatty liver and the final result depends upon the ratio between fat and lipotropic factors in the diet Thus a high fat diet in itself may not result in a fatty liver if the lipotropic factors are correspondingly increased On the other hand even a low fat diet may result in fatty liver if the lipotropic factor and proteins are very low (see Kwashiorkor) It is obvious that in man the deficiencies are not confined to one single substance but rather are due to a lack of several dietary substances and other factors such as infections toxins and anoxia exert their influence In addition to protein deficiency certain vitamin deficiencies undoubtedly play a role in man as well as in animal nutrition Vitamin B_1 is probably one of these vitamins

Over feeding or forced feeding in some animals such as the goose can cause fatty livers Such mechanism may play a role in human fatty liver but one cannot be sure that in man a deficiency in some essential substance may not enter into the picture Starvation is also productive of fatty liver but as is the case with vitamin deficiency diseases the abnormality is not as marked as in a deficiency of one food factor In starvation the metabolic demands are reduced and the needs for essential substances are drastically reduced So while starvation will result in a mildly fatty liver this will not be nearly as marked as in eucaloric diets deficient in lipotropic factors or proteins The starvation fatty liver is influenced by endocrine imbalance Extract of the anterior pituitary markedly increase liver fat accumulation in the starving animal

The mechanisms operating in producing the

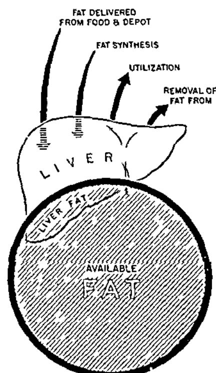


Fig 56 Th li r n b c nce ed flo ti g i a p l t f t which r p ents all of the a ilabl fat Normally th l r fat abo t 6% Th m l t t i ma n tain d b th t l c s acti g i quil br m The two rows p i t ng to th li r t in th d r ti of crea ng th l er f t (s bm rg ng th l v r de pe n the pool of f t) Th rr w p nt g aw y f m the l er r p ent t re s wh ch lift th l v r f om the fat p l a d d cre e the f t c nt nt of th li

nutritional fatty livers differ Thus in high fat low protein diet the diet is the source of the fat while in starvation fatty liver the peripheral depots are the source of the liver lipids In eucaloric diets poor in both fats and protein (Kwashiorkor) the fat must come either from the depots or from increased synthesis in the liver

There is a variation in lobular fat distribution which may depend on the mechanism involved In starvation where the source of the fat cannot be the diet the fat is chiefly in the periphery of the lobule while in fatty liver produced in the rat by high fat choline deficient diet the lipids accumulate centrolobularly The fatty liver that develops in the African natives on a high carbohydrate diet

shows the greatest accumulation of fat in the *periphery of the lobule* This suggests that if the liver lipids are from an exogenous source their localization is in the center of the lobule but when the lipids are endogenous the localization is in the periphery of the lobule

The fatty livers resulting from extensive pancreatic damage are related to the resultant *lipotropic factor deficiency* and therefore can be regarded as dietary in origin It is conceivable that the digestive disturbances in pancreatic achylia interfere with absorption or utilization of the factors required for keeping the liver lipids at a normal level and result in a dietary type of fatty liver

Toxins that produce fatty livers may act in this manner that is by interfering with the lipotropic activities of the liver

Anoxia of the liver whether due to partial decrease of oxygen pressure chronic anemia or *local interference with hepatic blood supply* results in fatty changes The inter relationship of the various causative factors is expressed in the theory that certain toxins cause hepatic injury by local ischemia A critical reduction of oxygen to the active hepatic cells interferes with fat utilization or perhaps results in increased production *Local ischemia could* hardly influence transportation of fat to the liver from distant depots and since increased fat in the diet is not necessary for its production the fault must be in the liver cell itself

Infections of various types may result in fatty liver *(Section VI) The pathogenesis* here may depend on several factors already mentioned During infection the diet may become deficient because of anorexia or vomiting on the other hand a deficiency may develop because of the increased metabolic rate and increased demand for foodstuffs Anoxia may develop especially in respiratory infections and some bacteria and their by products may have a toxic effect on the liver cell

The endocrine glands influence the deposition *of fat in the liver (Section X) The hormones* have a subtle effect on lipid metabolism in the liver and probably act directly on the intracellular enzymatic processes as well as on fat mobilization from peripheral depots The fatty *liver of diabetes is a classic clinical example of the relationship of* the endocrine glands to fatty liver, the fatty liver here is akin to that *in the starving animal* since severe, uncontrolled diabetes *is a form of starvation due to* wasting of calories in the urine Insulin stimulates deposition of fat in the *fat depots (lipogenic effect)* and at the same time removes fat from the liver (*lipokinetic effect*) *Anterior* pituitary extracts increase fat deposition in the periphery of the lobule and accelerate this process in starving animals *This suggests that* this hormone accelerates fat mobilization from the storage depots

Some recent work on the synthesis of fat by liver slices in a medium containing acetate *throws additional light on the problem and* indicates its complexity Liver slices from normal animals have the capacity to perform this synthesis but liver slices from pancreatectomized animals lose this function If simultaneous hypophysectomy is done lipogenesis by the liver slices is reverted to normal Purified anterior pituitary growth hormone injected into these animals subjected to pancreatectomy and hypophysectomy results in inhibition of lipogenesis Cortisone has the same inhibiting effect The inhibitory effect of *these hormones on lipogenesis in liver slices of* normal animals was also demonstrated The lipogenic effect of pancreas is probably due to insulin While these experiments show that endocrines have a direct effect on fat synthesis *by the liver* they *cannot be applied directly to the intact animal For in the intact animal* insulin tends to remove fat from the liver and cortisone has a tendency to stimulate fatty infiltration of the liver (Steinberg et al)

Clinical Features

Introduction

In spite of the complexity of the pathogenesis of fatty livers discussed above it is convenient for clinical purposes *to divide* these into two types the primary and secondary fatty liver By secondary fatty liver I mean one that is secondary to a well known clinical entity such as chronic infection, chronic anemia or diabetes mellitu In such *instances* the primary disease is most important and the major therapeutic attack should be directed

toward it with modifications directed to this complication The primary fatty liver is one which is not dependent upon another disease entity but is the major or sole clinical and anatomic abnormality It is usually dependent upon or caused by dietary insufficiency alcoholism (Fig 57) or chronic exposure to some toxin Occasionally the etiologic agent is not detectable and it remains idiopathic or truly primary This is a useful albeit arbitrary classification and remains flexible since a primary fatty liver may become secondary after the discovery of a hidden and previously undetected disease

Incidence

It is hard to delineate the exact incidence of fatty liver depending upon whether we refer to the primary or secondary type whether we are using autopsy or needle biopsy material and finally whether the liver is purely fatty or shows other changes indicative of degeneration or cirrhosis Secondary fatty liver in patients dying from chronic or prolonged infections is very common and may be as high as 50% In unselected autopsy material the incidence of fatty liver may be no more than that of cirrhosis Ulevitch and coworkers found fatty changes in 18% of 750 needle biopsies of the liver These patients however were a selected group in whom hepatic disease was suspected clinically My experience is roughly in agreement with that of Schiff s group who found fatty changes in one out of six (16%) biopsies The incidence of course rises markedly in geographical areas where malnutrition is widespread Dible did chemical analysis of livers of patients dying from various diseases and did not find a large amount of chemical fat in these livers Cirrhotic livers showed increased fat in over 40% of cases The incidence of fatty liver in obesity is of special interest because in them there is presumably an increased exogenous supply of fat Zelman s recent report of a small series of cases shows fatty metamorphosis in 50% This high figure is of further interest since fatty liver may be a precursor of cirrhosis and the mortality from cirrhosis in obese males is $2\frac{1}{2}$ times that of the rest of the population (Dublin and Marks 1952)

Symptoms

The history frequently reveals addiction to alcohol and/or a poor dietary intake especially as regards to proteins and vitamins Anorexia and weight loss are frequent complaints but obesity may be present Occasionally weight loss is complained of without anorexia but more often the reverse is true since the weight loss may be insignificant or obscured by water retention Nausea and vomiting are likewise frequent complaints especially in those with a history of alcoholism (Fig 57) Pain may be present and this is usually in the epigastrium or right hypochondrium but occasionally in the left hypochondrium The abdominal pain may be aggravated by food intake and exercise This suggests a relationship to pressure from the filled stomach Abdominal distention due to ascites or the hepatic enlargement may be the presenting complaint Bleeding tendencies such as epistaxis hematemesis or melena may occur Hematemesis may be due to associated pathology such as gastritis or peptic ulcer but when it is due to bleeding varices cirrhosis should be suspected Diarrhea occasionally accompanies the fatty liver

Physical Findings

Some of the patients may be obese, but the majority are not Most of the severe fatty livers I have seen were in thin individuals with very little adipose tissue contrary to Dible s impression

A palpable liver is the commonest finding and occurs in most patients Indeed it may be the only finding The liver may be markedly enlarged and extend to the umbilicus and across to the left side of the abdomen but may extend only 2 or 3 cm below the costal margin The liver is usually soft and non tender but occasionally tenderness is present and quite marked

Splenomegaly is a rare finding and when present it is not very large Ascites and peripheral edema are likewise uncommon Ascites was present in four of Ulevitch s patients and in one of our patients described below The ascites is associated with hypoalbuminemia

Jaundice of a mild degree is occasionally found and subsides rather promptly upon

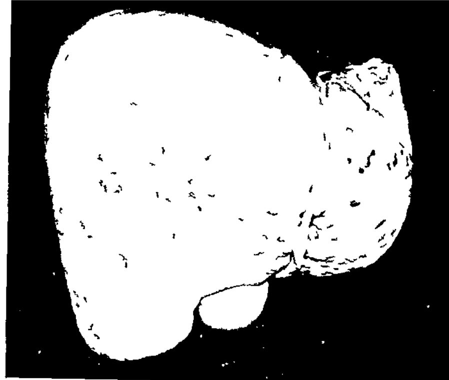


Fig 57 Marked fatty metamorphosis of the liver Microscopic section reveals marked fatty metamorph lymphocytic and polymorphonuclear cell infiltration Note the fatty cysts at FC

This male patient age 47 gave a history of alcoholism for 9 month vomiting months prior to admission abdominal pain nausea and vomiting 1 day Physical examination revealed icterus stupor palpable liver soft and very tender ascites Urine urobilinogen 1 4 mgm/1 0 cc positive for bilirubin Thymol turbidity 14 units Serum bilirubin 6 7 mg% direct 5 5 mg% Alkaline phosphatase 5 7 Bodansky units Total protein 6 3 gms Albumin 3 1 gms Globulin 3 gms

therapy in the adult In the fatty liver of the newborn the jaundice is progressive and may become very intense Spider telangiectasis may be detected in the presence of ascites Other evidence of malnutrition such as glossitis stomatitis and peripheral neuritis may be manifested in some cases A low grade fever may be present occasionally

Laboratory Findings

Liver function tests may be completely normal in spite of considerable fatty infiltration of liver The bromsulphalein test is most frequently abnormal but the flocculation tests cephalin cholesterol and thymol may likewise be abnormal The serum bilirubin is at times slightly elevated and when this occurs the urine contains bilirubin and excessive amounts of urobilinogen The serum albumin may be depressed—even markedly on occasion and there may be some elevation of the alkaline phosphatase and prothrombin time

Koch Weser and his coworkers found marked liver function abnormalities in experimental ethionine fatty liver which exceeded in some respects those seen in carbon tetrachloride necrosis They found that the bromsulphalein retention and hyperbilirubinemia were more marked in the uncomplicated fatty liver than in the one showing necrosis and explained it on the basis of changes in the intrahepatic circulation The alkaline phosphatase was elevated only in the animals with necrosis

The clinical and laboratory picture may therefore simulate cirrhosis and the exact diagnosis may depend upon liver biopsy as is demonstrated by the following case

Case 9

A Negro female age 35 entered the hospital on April 24 1951 complaining of recurrent swelling of the abdomen which began 12 weeks before The abdominal swelling apparently disappeared and reappeared 1 days before the first admission to the hospital At the onset the patient had several episodes of epistaxis and during one of them had a tarry stool She also complained of severe aching in the upper abdomen and pain radiating to both upper quadrants The pain was worse after eating and improved in the recumbent position She disclaimed anorexia but food intake was reduced because of pain Menstrual periods occurred regularly but were of shorter duration

Excessive alcoholic intake was denied and there was no history of exposure to toxins drugs or injections The diet appeared to be adequate but the patient disliked meats and therefore her protein intake may have been suboptimal

Physical examination revealed a thin undernourished female who appeared ill Her skin about her chest and shoulders showed areas of depigmentation Atypical spider telangiectasiae were seen over the posterior aspect of both arms The abdomen was distended with ascitic fluid and revealed some visible lateral abdominal veins The liver extended down to the umbilicus and across the midline to the left side of the abdomen This organ was firm and quite tender to palpation Some tenderness was elicited on the left side of the abdomen and after paracenthesis of 1400 cc of straw colored fluid the edge of the spleen became palpable

Needle liver biopsies were obtained with the Vim Silverman needle through the anterior abdominal approach The first one done April 7 showed marked fatty metamorphosis (Fig 58a) A specimen obtained May 25 still showed fatty metamorphosis which had markedly decreased On June 2 the liver biopsy showed that the fatty metamorphosis was replaced by alterations indicative of portal cirrhosis (Fig 58b)

The patient was treated with a high carbohydrate high protein diet restricted in fat and received supplementary multi vitamin preparations choline chloride 4 0 gm a day and . cc crude liver extract intramuscularly For several days the oral intake was supplemented with 1000 cc of 10% glucose in water Vitamin K 10 mg were given subcutaneously daily The salt intake was moderately restricted The patient ate well and after one paracenthesis the ascites did not recur The abdominal pain and the low grade fever disappeared The liver decreased in size and its tenderness subsided

Liver function tests are tabulated in Table 5 also showed progressive improvement



Fig 58 A Needle liver biopsy (× 100) showing severe fatty infiltration
B Needle biopsy of same patient three months later shows portal cirrhosis Case 9 page 307

On a subsequent admission on October 19 1951 the patient had a prolapsed intervertebral disc removed under spinal anesthesia from which she recovered uneventfully The liver was palpable about 3 cm below the costal margin on deep inspiration there was no tenderness and the spleen was not palpable

Liver function tests were normal except for

TABLE 5

Laboratory Data in Patient with Fatty Cirrhosis

Date	Total Protein	A/G	Serum Bilirubin	Cholesterol F ter %	Cholesterol mg %	T T	T F	C C F	Alk Phosph	Prothrombin time
4 5	7 1 gm	7/4 4	4 6 mg	18/mg	58%	4 8 u	+	+	9 4	18 2 sec
5-4	7 0	2 5/4 5	2 2	153	58% F	3 4 u	2+	1+		16 1 sec
5 15	7 95	3 0/4 95	1 4	185	66% F	4 2 u	2+	4+	5 0	
5 1	7 6	9/4 7	1 0							
	a0 9	β1 85								
		γ1 95								
5 8	7 3	75/4 55	0 85	149	60%	4 3 u	4+	3+		
	Bromsulfalein retention 16% in 45 minutes									
6-11	7 6	2 9/4 75	0 45	153	61 4%	3 7 u	2+	1+	4 5	

Other laboratory tests including serum chlorides sodium potassium glucose urea nitrogen CO_2 combining power were normal. The urine showed the presence of bilirubin and urobilinogen was positive in dilutions above 1 0

X-ray examination of the gastrointestinal tract was negative for esophageal varices and peptic ulceration

slight increase in the total and gamma globulin The albumin was 3 5 gm against 3 8 gm for the globulin

Differential Diagnosis

This case demonstrates several salient features about the differential diagnosis of fatty liver In the differential diagnosis one has to consider all the conditions that may be accompanied by hepatomegaly but especially cirrhosis The above patient had all the clinical and laboratory findings of cirrhosis but two successive biopsies showed fatty metamorphosis Liver biopsy is therefore an indispensable procedure for diagnosis The third biopsy showed evidence of portal cirrhosis (Fig 58b) This is an example of fatty liver progressing to portal cirrhosis The unusual feature is the short time interval Of course the possibility exists that the features indicative of cirrhosis were not demonstrated in the first two biopsies In spite of this possible confusion a biopsy still serves a practical purpose since the prognosis is better in fatty liver and the treatment is slightly different

Since fatty liver accompanied by jaundice is seen in the newborn it has to be differentiated from the more common causes of jaundice at an early age namely erythroblastosis fetalis and atresia of the extrahepatic bile ducts and von Gierke s disease The age of onset may be different in the first two however fatty liver may also begin in the neonatal state but the hematologic picture Rh agglutinins and groupings in the parents should establish the diagnosis and the evidence of complete extrahepatic biliary obstruction should help to establish atresia of bile ducts (p 93) Von Gierke s disease may be more difficult to differentiate but the attacks of spontaneous and induced hypoglycemia and acidosis should help to establish this diagnosis Needle liver biopsy would be equally valuable in infants but cannot be performed safely

Treatment

Lipotropic Substances

The object of treatment is to remove fat from the liver and re institute the normal hepatic histology and physiology With the tremendous amount of experimental work done on lipotropic agents and their effectiveness in dietary fatty liver in animals it is only natural that clinicians should turn to these substances in the treatment of fatty liver however the only type of fatty liver that choline (the most important of the lipotropic substances) can cure is the one due to choline deficiency It is likely that at least some of the fatty livers in man are due to choline deficiency but in the fatty livers of prolonged infection or those due to toxins no deficiency of choline in the diet can be postulated and therefore no beneficial effect from choline can be expected Indeed it has been pointed out that in the deficiency fatty liver seen in Kwashiorkor choline is ineffective The only logic for using choline in fatty livers where a choline deficiency cannot be demonstrated or assumed is that there may be abnormal absorption or utilization and

therefore added choline in pure form may be useful The evidence in favor of such possibility will be discussed later

The next question to be answered in regard to the use of choline and other purified lipotropic agents such as methionine is whether *they are necessary or beneficial when the diet* contains an abundance of these substances The obvious answer is No! However the obvious answer is not necessarily the correct one In certain specific instances in animals and man choline is definitely needed in spite of a complete diet Such is the case in pancreatectomized dogs and in human subjects with pancreatic insufficiency in whom the lipotropic substances cannot be digested and absorbed because of lack of proteolytic enzymes In the presence of a supposedly normal digestive and absorptive mechanism and an adequate diet added lipotropic substances may not be necessary but there is some evidence which will be recounted shortly that these substances may nevertheless have some rational use

I am in favor of using choline or methionine They are entirely harmless and there is some evidence that they are beneficial over and above an adequate diet and the diet may not be consumed by the patient in sufficient quantities Medical history is replete with discarded *empirical remedies* which have returned into good graces because of experimental evidence of their usefulness Choline can be used in tablet form as the chloride or carbonate or in the form of a 25% syrup of choline dihydrogen citrate The daily dose is 4 to 6 gm divided into three or four equal portions Methionine is administered in 0 5 gm tablets for a daily dose of 3 to 6 gms Figure 59 shows the disappearance of fat from the liver on a nutritious diet supplemented with lipotropic substances

Diet

The diet should be high in proteins of good quality such as meat and fish A protein intake of 150 gm a day should be aimed at The bulk

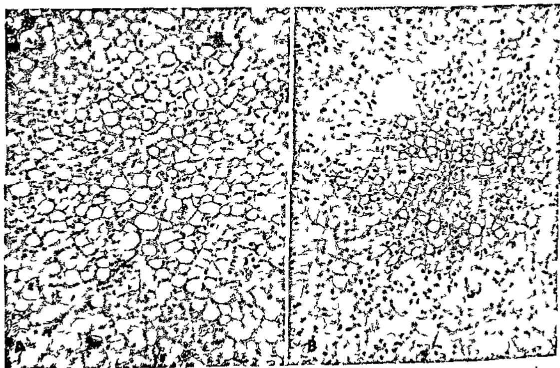


Fig 59 A Needle biopsy of liver (× 140) showing marked fatty metamorphosis The patient was an alcoholic who neglected his diet The liver was enlarged

B Same patient after 3 weeks on a high protein diet supplemented with lipotropic substances Biopsy of liver shows marked decrease of fat

of the calories should be provided by carbohydrates and therefore this should be close to 350 gm a day The dietary fat should be kept at a minimum Since a palatable natural diet high in protein cannot be devised fat free at least 70 gm of fat must be included I cannot see how one can condone a high fat diet especially in fatty liver What is the logic of supplying more of the substance that we are trying to remove from the liver? When some of this exogenous fat reaches the liver it requires more lipotropic substances and makes the object of therapy more difficult The diet should be low in salt if there is evidence of edema or ascites

Vitamins

Vitamin supplements and liver extract may be utilized as in cirrhosis

Intravenous Alimentation

Intravenous glucose can be usefully and conveniently administered when the caloric intake is deficient I prefer using 10% glucose If there is evidence of water retention saline should be avoided

Bed rest should be maintained if there is jaundice or when the liver is tender and there is considerable disturbance in liver function tests

43 *The Rationale of Using Lipotropic Factors and Tocopherol in Clinical Liver Disease*

Lipotropic Factors

I HAVE pointed out previously that the use of the innocuous lipotropic substances choline and methionine is advisable in fatty liver in addition to a high protein diet and in spite of the lack of clear cut evidence pointing to lipotropic factor deprivation as a cause of the fatty liver

Cayer and Cornatzer in a series of studies utilizing radioactive phosphorous to determine plasma phospholipid turnover found that administration of a single large dose (10 gm) of choline did not influence phospholipid turnover in a normal individual Normal individuals placed on a low protein diet for seven days showed no evidence of choline deficiency as demonstrated by a lack of acceleration of phospholipids turnover after test dose of choline However patients with large fatty cirrhotic livers showed a significant increase in phospholipid turnover to a test dose of choline or methionine The stimulating effect of the lipotropic agents on phospholipid turnover continued in spite of a high protein diet for several months or until the liver lipids have decreased as evidenced by liver biopsy One patient with a fatty liver who did not respond to choline died This suggests that the non stimulation of phospholipid turnover by choline in a fatty liver is indicative of grave damage and a poor prognostic sign Patients with hepatitis and cirrhosis without fatty infiltration likewise showed no response This is to be expected since these livers contained a normal amount of fat

Pelner and coworkers reported that normal individuals receiving a 10 gm test dose of choline orally do not show any urinary excretion of this substance while patients with cirrhosis showed urinary excretion the intensity of which paralleled the severity of the disease As the patient improved the urinary choline

excretion decreased and vice versa They found a similar response in patients with gastrointestinal cancer They postulate that liver damage is responsible for this phenomenon which is based on the inability of the organism to utilize properly the free methyl group They cite the work of Castro Mendoza who found a similar increased excretion of choline in liver damage in man and dog It is odd however, that this disturbance was not found in hepatitis where the liver dysfunction is greater than in neoplasms of the gastrointestinal tract

Observations made in Popper s laboratory (de la Huerga et al) did not confirm the above experiments These workers found no choline in the urine in normal individuals or patients with hepatobiliary disease under basal conditions and only minute amounts (less than 0 3% of administered dose) after test dose However about two thirds of the choline N was found in the urine of normal individuals as trimethyl amine In liver disease the urinary excretion of trimethyl amine is delayed or decrea ed Since incubation of choline with feces results in the formation of trimethyl amine they conclude that this transformation occurs in the gastrointestinal tract by bacterial fermentation and that the difference in response between the normal individuals and those with liver disease is dependent upon a difference in the intestinal bacterial flora Thus in normal individuals choline administered by mouth is not absorbed but changed to the inactive trimethyl amine but in liver disease there is increased absorption of choline presumably because of the altered intestinal bacteria Administration of aureomycin concomitantly with choline aid its absorption by changing the bacterial flora

These deductions were strengthened by experiments in which the choline was administered intravenously On administration of choline by this route the urinary trimethyl amine was not increa ed significantly However 9% of the intravenously administered choline was excreted in the urine of the normal subjects but twice this amount was lost by patients with hepatitis but not by those with cirrhosis This again shows a difference in response to administered choline by patients with liver disease It is reasoned from these experiments that patients with hepatitis ar[e] capable of utilizing choline properly while [pa]tients with cirrhosis may have an incre[ased] demand for this substance

It seems therefore that there is some [ab]normality in utilization of choline in pat[ients] with liver disease and a mechanism of prot[ect]ing the intestinal absorption of this substa[nce] Carbohydrates seem to impede this intest[inal] inactivation and antibacterial agents do by inhibiting the growth of the respons[ible] bacteria Choline can apparently be adm[inis]tered safely intravenously by diluting 1 2 0 gm of choline base in 500 or 1000 cc of glucose

Methionine functions as a lipotropic ag[ent] by virtue of its conversion to choline in [the] body In view of the possible inactivation [of] choline in the human gastrointestinal tr[act] one wonders whether methionine may not [be] better absorbed and hence, more active a[s a] lipotropic agent than orally administe[red] choline Methionine of course has anot[her] function in liver disease because of the S[H] group

Are there rational reasons for administeri[ng] this amino acid as a supplement to a diet ad[e]quate in proteins? Kinsell and cowork[ers] found removal of intravenously injected m[e]thionine impaired in patients with liver d[is]ea[se] hence abnormal utilization is postulated Th[ey] also found that both methionine and choli[ne] have a protein sparing effect even in the pre[s]ence of a high protein diet in patients wi[th] chronic liver disease In acute liver diseas[e] this effect wa not so clear The effect of choli[ne] is explained on the basis of making more m[e]thionine available for other metabolic purpose[s] These observations were made in patients wi[th] non fatty livers and hence the effect was n[ot] lipotropic in nature

The effect of lipotropic agents on clinic[al] cirrhosis and other type of hepatic injury h[as] been reported by many observers These ob[ser]vations consist of following the rate [of] clinical improvement and/or the results of live[r] biopsy It is generally agreed that in the earl[y] or fatty phase of hepatic cirrhosis there [is] both clinical and histological improvement o[n] a high protein diet Some maintain that th[e]

impro ement s more rap d w th the add t on of l potrop c agents wh le others have observed no add t onal effect n the presence of an ade quate d et (Post et al 195) In a chron c d sease such as c rrho s cl n cal ob ervat ons that are d fficult to control cannot be expected to y eld absolutely ncontravert ble results So wh le the re ults of added l potrop c agents are not dramat c there s at least suggest ve ev dence that they may speed recovery

Meth on ne would be expected to have so ne protect e effect aga nst hepat c necro s Such protect ve effe t aga nst hepatotox c agents has been suggested by ob ervat ons n man (p 179) Infect ous hepat t s n wh ch fatty cl ange are not part of the p cture cannot be expected to respond to l potrop c agents but a sulfur con ta n ng am no ac d such s meth on ne has an ant necrotogen c effect Popper and co workers foun l no ev dence of a prote n spar ng effect from meth on ne n four pat ents w th acute hepat t s Object ons may be ra sed aga nst conclus ons dra vn from such a small group Strom found that 5 gm of meth on ne g ven da ly to 1 5 pat ents w th hepat t s re sulted n suppress on of hyperb l rub nem a and more rap d d sappearance of jaund ce and hyperurob l nogenuria However there s some quest on about the stat st cal s gn ficance of the results n the treated as compared w th the control group

Tocopherol

S nce the defic ency of tocopl erol n an mals may re ult n hepat c necros s and tl s v tam n can be used to prevent it t s appl cab l ty to l ver d mage n man comes under scrut ny The exact requ rements of th s substance for man s not known but H ckman an l Harr s n the r splend d rev ew nd cate that some here between 11 7 and 59 mg of alpha tocopherol the m n mal da ly requ rement The d vergence of these two figure is due to the d fferent approaches n calculat ng the human requ e nent from an mal exper ments It s est mated that the average adult requ res at least 25 mg of tocopherol da ly but the average Ame can consumes about 15 mg da ly and part of th s s the gamma form wh ch is nactive as far as the protect ve effect on the l ver s concerned It is surpr s ng therefore that v tam n E defic ency is not more fre quently observed However the obs rvat on tl at some forms of Dupuytren s contracture respond to v tam n E adm n strat on nd cates that such defic ency does occur and th s syndrome an example of t

Low blood tocopherol levels have l een ob served n pat ents w th l ver d ea e b seve al nvest gators (Klatsk n et al 1950 1751 and Popper et al 1949) Wh le these plasma levels were cons derably belo v that of normal adults depres ed plasma level was al o not ced in pa t ents convalesc ng from non hepat c d seases Oral tocopherol toleran e tests gave flat plasma curves suggest ng defe tive absorpt on There as ho e er no relat onsh p bet veen the degree of plasma level depress on and the sever ty of l ver d sease and further stud es nd cated that c rrhot cs are capable of absorb ng th s v tam n n a normal fash on The lo plasma le els appear to be related to a de fic ent ntake

If we comb ne th s ev dence of defic ent plasma levels and low t s ue stores of v tam n E n pat ents w th c rrhos s and the exper

Tab e 53

D a F Re a d o Li l j y nd he Po b e The apeu c Impl ca on

D y F	Immedia	U p l y L m
Lipo op c F ors		
Chol n	Fa L e	Fa n
B ne		onal (Laen
Me h n ne		nec s) c
Lec h n		rho s
Pr e n		
Ino l?		
*Th am ne	Th m ne	
	Fa y l v r	
B o n	B o n	
	Fa y l e	
Cys ne	H pa c nec o s	Po ne o c
M h or ne		c rrh
Alpha T coph er l		
B Comp x	H pa c n o s	
B	Lipo p c eff ct pro ec ag n t po ons	
Fol c Ac d	Ac syne g ca l w h B	

The p e en e of h sub an es c le a es he effect of defi ency of l po rop c s b an s

mental evidence of its relationship to hepatic necrosis we have a good case in favor of its use in supplementing the diet in liver disease. Its chief use would be in hepatic necrosis such as is seen in infectious hepatitis rather than in fatty cirrhosis The dose of 200 to 300 mg a day is not excessive since we are trying to fill the depleted stores Similar dosage levels have been used in Dupuytren s contracture Table 53 enumerates the various dietary factors that are related to hepatic injury and their possible therapeutic implications

44 *The Relationship Between Pancreatic Disease and Liver Disease*

THE discussion of the relationship of pancreatic to liver disease in man is appropriate at this point in view of the experimental evidence pointing to dietary deficiency as the mediating factor in this relationship We are interested here primarily in the non insulin secreting portion of the pancreas and the relationship of diabetes to liver disease is discussed elsewhere (p 460) The questions that we would like answered are (1) does pancreatic disease result in liver disease in man? (2) how frequently does this occur? and (3) does liver disease produce pancreatic disease?

Experimental evidence indicating that pancreatectomy or the loss of external pancreatic secretion in the dog results in fatty liver which is due to malabsorption of lipotropic factors has also been discussed in the preceding section Kwashiorkor a disease in man has its starting point in dietary deficiency which leads to pancreatic damage (external secretions) this in turn leads to further dietary deprivation with final breakdown of liver physiology These two experiments one in the laboratory the other in nature emphasize the pancreatico hepatic axis The association of pancreatic and hepatic damage on a dietary basis have also been demonstrated by Friedman and Friedman in the rat and Lindsay and co workers in the dog The latter experiments are of particular interest since pancreatitis was produced by a high fat low protein diet and this was followed by fatty liver It is of interest that ethionine which has recently been used in the production of fatty liver, also produces pancreatic fibrosis (Goldberg and Chaikoff) Specifically does chronic cystic fibrosis of the pancreas chronic pancreatitis relapsing pancreatitis or pancreatic lithiasis contribute to formation of fatty liver or other types of liver injury?

Childhood Form of Cystic Fibrosis of Pancreas

Loss of Pancreatic Enzymes

Cystic fibrosis of pancreas a rare disease seen in childhood is frequently accompanied by hepatic injury Andersen s review of 49 cases in 1938 brings out this point very clearly In this group of patients 31 or over 63% showed some liver abnormality Fatty liver was found in 18 hemosiderosis in 13 portal cirrhosis in and biliary cirrhosis in 1 One liver was described as jaundiced Bagenstoss and Kennedy found a fatty liver in 50% or 7 of their series of 14 patients but the degree of involvement was described as mild in four Individual case reports are found in the literature emphasizing

this relationship (Thomas and Schultz 1938 Pugsley and Spence 1949) In juvenile diabetes fatty livers have been described which apparently depend on derangement of the non insulin secreting portion of the pancreas (Grayzel Radwin 1938 Marble et al 1938)

The frequency of concurrence of pancreatic and hepatic disease in childhood is so great that one is forced to assume some cause and effect relationship It is very tempting in deed in view of animal experiments to postulate that the pathogenesis in children is akin to that in the depancreatized dog Some of the observations in children as well as adults that lipocaic resulted in reduction in size of these livers seemed to confirm this theory

Malnutrition

The finding of hepatic hemosiderosis in addition to fatty liver (Andersen) brings to mind the nutritional hemosiderosis observed by the Gillman s in African natives who also showed pancreatic disease This introduces the possibility that malnutrition may be responsible for both the pancreatic and hepatic damage At any rate the general nutritional failure in chronic pancreatic disease may be a factor in the ultimate liver damage

Infection

Infection is probably the third factor which contributes to the hepatic changes Almost invariably these infants have severe pleuro pulmonary inflammatory changes pleuritis purulent bronchitis bronchiectasis and pulmonary abscess all these may secondarily damage the liver The case reported by Pugsley and Spence is of particular interest in regard to the pathogenesis of the liver disease This patient with cystic fibrosis of pancreas lived to the age of 17 and showed well developed hepatic cirrhosis Grossly however the liver showed the large nodules of a post necrotic rather than a fatty (nutritional) cirrhosis This patient suffered from pulmonary inflammatory disease for seven years prior to death, and this chronic infection was probably an important contributing factor in the liver disease

It is therefore logical to conclude that liver disease in childhood cystic fibrosis of pancreas is dependent on the following three factors acting synergistically and with varying force to produce the liver disease (1) loss of external pancreatic secretions (2) malnutrition and (3) infection

Adult Form of Pancreatic Lithiasis Chronic Relapsing Pancreatitis

Chronic as well as acute pancreatitis may produce post hepatic jaundice by compressing the common duct This problem is discussed on page 127 Here we are interested in the parenchymatous hepatic changes produced by more subtle and elusive factors In 11 of 21 cases of relapsing pancreatitis the serum bilirubin was slightly elevated (up to 3 mg) in only one was the hyperbilirubinemia considerable (to 8 mg) The chief responsible factor for hyper bilirubinemia is probably compression of the common duct

The interest in the development of fatty liver in patients suffering from diffuse pancreatic disease was stimulated by the experimental work on fatty liver by Dragstedt and others in the 1930 s During that period case reports appeared in the literature dealing with fatty livers in patients with pancreatic disease These reports included two cases of pancreatic lithiasis (Snell and Comfort 1937) one case each of pancreatic atrophy secondary to carcinoma of pancreas (Norris et al 1938) pancreatic disease associated with cholelithiasis (Rosenberg 1938) and two cases of pancreatic fibrosis and atrophy (Cole and Howe 1940) All of these patients had fatty livers and some of these apparently responded to pancreatic extract (lipocaic)

In the more recent larger groups of patients the frequency of association of fatty liver with diffuse pancreatic disease has been confirmed Edmondson and coworkers (1950) found a fatty liver in 17 (65%) of 26 patients with pancreatic lithiasis and chronic pancreatitis Sanes and coworkers (1950) found fatty changes and/or cirrhosis in all of seven cases These studies were in postmortem material

The evidence of this association is not so startling in clinical material but this avenue of approach may be amplified by more frequent use of needle biopsy Hepatic disturbances were

noticed by Comfort and coworkers in several of their cases of relapsing pancreatitis that *could not be attributed to compression of* common duct In two patients although the liver looked grossly normal at surgery there was clinical evidence of hepatic dysfunction I have frequently observed mild bromsulphalein retention depression of serum proteins and mildly positive flocculation tests in relapsing *pancreatitis especially during or shortly after* the acute episodes

Again we are faced with the problem of the pathogenesis of the hepatic lesion Direct dependence on the diffuse pancreatic disease and the pancreatic achylia is a likely possibility however before we can accept the pancreatic *disease as the sole or even most important* factor in the pathogenesis of the liver disease it must be established that (1) the pancreatic disease precedes by a considerable period of time the hepatic disease and (2) the fatty liver which follows the diffuse pancreatic disease is ameliorated by lipotropic substances *and or active pancreatic enzymes*

In the state of our present knowledge other etiologic factors must be considered as contributing to the pathogenesis of liver injury in diffuse pancreatic disease Alcoholic excesses are elicited in the history of many patients with relapsing pancreatitis I found this so often that I *hesitate to make a diagnosis of chronic re*lapsing pancreatitis unless a history of alcoholism is obtainable The history of alcoholism in chronic pancreatitis and pancreatic lithiasis is stressed by many authors 53 8% of Edmondson s cases had a history of alcoholism 68% of Comfort s group used alcohol and 3-% used it excessively Alcohol has been stressed as an etiologic agent in the pathogenesis of pancreatitis by various writers (Weiner and Tennant 1938 Clark 194-) most recently by Stinson and coworkers Since alcoholism with its concomitant malnutrition is an established factor in the pathogenesis of cirrhosis and fatty liver the pancreatitis as well as the liver injury may be caused by this agent

Dietary insufficiency may become important after chronic relapsing pancreatitis and pan*creatic lithiasis has become established* and this independent of alcoholism These patients with their recurrent bouts of pain vomiting and dyspepsia are subjected to frequent periods *of inanition and these periods of malnutrition* may be etiologic in the hepatic injury The steatorrhea and azotorrhea may also interfere with absorption of nutrients

Infection may also play a role since the pancreatic disturbance may be primarily or secondarily inflammatory Moreover the frequency of gall bladder and biliary tract inflammation and disturbance may result in hepatic disturbance Other infections may also be superimposed in advanced cases

Therefore we must conclude that in the adult type of diffuse pancreatic disease liver involvement is common and the liver disease is due to (1) loss of pancreatic enzymes ( ) alcoholism (3) dietary abnormality (4) infection in the biliary tract pancreas and elsewhere

The Role of Chronic Pancreatitis in the Production of Cirrhosis

Although there is enough evidence that chronic pancreatic disease is productive of liver damage there is little evidence that pancreatic disease is etiologically important in *the production of cirrhosis Stinson* in a study of pancreatic lesions associated with cirrhosis found that neither by their extent or nature could the lesions of the pancreas be held responsible for the cirrhosis However with the increasing frequency of chronic pancreatic disease a closer etiologic relationship to cirrhosis may yet be established

Influence of Liver Disease on Pancreas

Some evidence may be adduced from the literature that liver disease is etiologic in the production of pancreatic disease Over 50 years *ago Steinhaus described interstitial* fibrosis of pancreas in 11 of 12 cases of cirrhosis Kirshbaum and Shure in an autopsy study of 356 cases of cirrhosis found pancreatic fibrosis in 36 2% However Stinson and associates found changes in the pancreas as frequent in 75 controls as in 75 patients with cirrhosis The greater frequency in the cirrhotics of certain types of changes are explained by them not as a cause

and effect relationship but on the basis of a common etiologic factor The steatorrhea of liver disease has been erroneously assumed to be due to possible pancreatic damage However recent clinical studies do not indicate pancreatic insufficiency in parenchymatous liver disease Gross and coworkers found the external pancreatic secretion normal in patients with liver disease both before and after secretin stimulation Elevations of serum lipase and amylase were found in some cases of hepatitis and cirrhosis by Cummins and Bockus The significance of these enzyme elevation is unknown but they cannot be attributed to pancreatic disease The liver itself may be responsible for these changes since it elaborates amylase and may have some controlling influence on serum lipase The elevation of these enzymes in acute liver disease may cause diagnostic confusion There is no clear cut evidence that liver disease causes direct pancreatic injury but it is conceivable that disturbance of portal circulation and the metabolic derangement that follows severe liver destruction may produce an untoward influence on the pancreas The effect of liver disease on diabetes and carbohydrate metabolism is very definite and is discussed on page 463

VIII ANATOMY OF THE LIVER AND ITS VASCULAR SUPPLY—DISEASES OF THE LIVER RESULTING FROM DISTURBANCES IN THE MAJOR VESSELS

45 — *Gross Anatomy of the Liver and its Anomalies*

THE liver is the largest gland in the body weighing 1400–1600 gms in the adult male and is slightly smaller in the female It comprises about 1/40 of the adult body weight but is relatively larger in the fetus in which it is about 1/20 of the body weight It occupies the right upper portion of the abdomen and extends slightly over to the left of the midline

ATTACHMENTS AND LIGAMENTS

It is firmly attached to the diaphragm by the falciform ligament which is a triangular fold of peritoneum The free inferior portion *of the falciform ligament ends in a rounded* cord the ligamentum teres (round ligament obliterated umbilical vein) The superior posterior portion of the falciform ligament branches to right and left forming the corresponding right and left triangular ligaments which also anchor the liver to the diaphragm These ligaments also attach the liver to the anterior abdominal wall The coronary ligaments anterior and posterior are situated on the posterior and inferior surface of the liver and complete the attachments to the abdominal wall and diaphragm The hepatogastric ligament attaches the liver to the lesser curvature of stomach and the hepatoduodenal to the duodenum

LOBES OF THE LIVER

The line of attachment of the falciform ligament divides the liver into a right and left lobe The right lobe is much larger This division into a right and left lobe is important physiologically as well as anatomically because of the streamlining of the portal circulation which makes the two lobes functionally independent (p 32-) Two other small lobes are described *which are really subdivisions of the right* lobe namely the caudate and quadrate lobes The caudate lobe is situated on the superior posterior surface of the liver adjacent to the inferior vena cava The quadrate lobe is situated at the anterior inferior surface of the liver between the round ligament and the gall bladder

The liver is a wedge shaped organ The right lateral portion is the thickest and it tapers toward the left It is interesting and practical in view of the increasing use of punch biopsy to note its various measurements (1)

vert cal near r gl t lateral s rface 15 to 17 5 cm (2) greate t anteroposter or measurement at level of pole of r ght k dney 10 to 1 5 cn (3) anteroposter or d in eter n the m dl ne oppos te verteb al col n n s reduced to about 7 5 cm

CLINICAL DETER INATIO OF I VER S ZE

The norn al l ver extends fron the fifth or s xth intercostal pace n the r ght m dclav cu lar l ne down to the r ght costal marg n In e t mat ng tl e s ze of the l ver one must always determ ne ts upper border by per cu s on s nce palpab l ty of the l er belo the costal narg n may be due to d splace nent do nard In any norm il n l v duals the l er palpable 1 to 3 cm below tl e r ght costal marg n on deep n p rat on Therefore a palpable l ver cannot be cons dered enlarged e en when tl e upper border is at the normal level The cl n cal determ nat on of l ver s ze s so fallac ous th t a palpable l er may be normal n s ze maller or larger than normal One cannot call a l er enlarge l w th any degree of assurance unle t extends more than 4 cm belo the co tal marg n and the upper border s at the fifth ntercost l space n the m dclav cular l ne Even th cr ter on nay somet mes be erroneous

D pla ement of the l er lownward ma be p oduced b (1) e phy ema (2) subphren c accu n lat on of flu d (3) r ght s ded ple ral effus on an l l ydrothorax D placement of the l er l an e pl y e natous lu g can be de tected b the downwa d d place ent of the upper border of l er l lne s S bphren c ac c mulat on of flu d sucl a n s bphren c ab ces d ffi ult to d st ngu h cl n cally from l epat c enlargement H e e ome a d n ay be ol ta ed by roentgenograpl y (See Cl apter 26) In s bphren c ab es the r ght d aphragm s nmol le th s al o true la ge hepat c ab ces es but does not occur n other causes of l ver enlargement Ple ral effu on can u ally be d agno e l fro tl e phys cal exam nat on of the chest

X ray deter n nat o of the l ver shadow may be u ed a a mea ot e t nat ng the s ze of th s o gan but th s n ethod s l o fall ble The pla n fil of abdo en to deter n ne the lower l o de of the l ver s n my exper ence qu te inaccurate and frequently shows no correlat on w th the cl n cal find ngs Enlargement of the l ver up ward with concom tant elevat on of the r ght d aphragm can be effect ely den onstrated by chest x ray T mors (Chapter 19) and abscesses (Chapter 6) can l e lemonstrated by th s nean Certa n ano nal es of the l ver can also be den onstrated n tl s manner

Z lman (1951) recon mended mpro ing v s ual zat on of the l ver and spleen by fill ng the sto a l an l colon ith ga The pat ent ngests a substance such as Se ll tz powder to fill the stomach th gas and the colon s filled w th gas by nflat ng t through tl e anus The pat ent s exa ned in the upr ght po t on v th the x ray tube placed 40 ncl es from the target The poster or anter or v e s used for tl e l ver an l the left obl que for the pleen

Opac ficat on of the l er w th tho otrast (collo dal thor um d ox de) g en ntravenously has been all but abandone l because of ts po s ble dangers Another procedure for v sual za t on of the l ver and spleen by opac ficat on s descr bed on pag 4 0

ANO IALIES OF THE LIVER

Cullen n h s co nprehens e rev e v of ano nal es of the l ver a lopts Jacquemet s class ficat on as the ost adequate

Classifica to t of A omal es of Liver (Jacq eme t)

G o p A L mod fied n form nd d m n n	I pl e	a mod fi on b d m nu on b mod fi on b n a g m n c mod fic on d c o a on n con en p
	M p aced	a mod fi a on b d m n n b m d fi a n b n c a e c mod fica on d to a a on n c n t en pa

Group B		
L er ne h mod fi d f m or s d men n	M pla ed	Va a ons that ccom pan h s anomaly

A Liver Modified in Form and in Dimensions

1 Retaining normal place in abdomen In this group the anomalies may consist of reduction or increase in size of one of the lobes The left lobe may be diminished in size consisting of a flat band of hepatic tissue The atrophy may involve the right lobe but this is more rare On the other hand one of the lobes may be markedly hypertrophied and the other lobe normal in size Atrophy of one of the lobes in an adult is usually due to inflammation or vascular interference It is conceivable that a congenital atrophy may be due to intrauterine disease especially involving the blood supply

The liver may be modified in form Incised liver has been described which consists of a furrowing of the surface of the liver This is thought to be due to pressure of the diaphragm on the hepatic parenchyma This anomaly is more common in males

One of the modifications of form which can be grouped under hypertrophied lobes is the so called Riedel s lobe This was originally described by Riedel of Jena This anomaly consists of a marked elongation of the right lobe forming a tongue like projection into the lower abdomen and even into the pelvis Because of the unusual position of this lobe it has been mistaken for a ptotic kidney and a neoplasm Riedel s lobe has frequently been found adherent to the colon or cecum by adhesions and it has been postulated that these adhesions have been instrumental in pulling a portion of the liver down with formation of this anomalous lobe

Multilobulated livers or livers with accessory lobes are of greater clinical interest than the variations mentioned above These anomalies may assume many bizarre forms The accessory lobes are in most instances a subdivision of one of the normal liver lobes The attachment of the accessory lobe may be by a pedicle of liver tissue or mesentery The mesenteric attachments consisting of whitish fibrous sheets give the organ an odd appearance The accessory lobes may be single or multiple and vary in size from a small nipple like or tongue like projection to that of an average lobe Cullen reproduced a picture of a liver with sixteen lobes The deep fibrous tissue bands between the various lobes give the liver an appearance of hepar lobatum or a post necrotic cirrhosis with massive nodular hyperplasia It is possible that these anomalies have been created in some instances by a chronic inflammatory process Palpation of such a grossly irregular liver would cause much diagnostic confusion but such marked lobulation is a medical curiosity

Accessory lobes of the liver at the diaphragmatic surface cause a bulge in the diaphragm and projection into the right lung field presenting a diagnostic problem Tumor of the base of the lung tumor of the diaphragm and tumor of the liver have to be considered in the differential diagnosis Friedman and coworkers in 1947 reported this anomaly in a child They claimed that only 15 such cases have been reported in the literature This gives a false impression of their rarity Many of the subdiaphragmatic accessory lobes are not reported Two other cases have been reported recently, one each by Hardisty and associates and Katz and Williams I have observed one such patient for a period of years

Pneumoperitoneum helps to exclude the supradiaphragmatic position of the mass and places it in the substance of the liver However the possibility of its being a hepatic neoplasm cannot be ruled out except by exploratory surgery Hardisty and coworkers explored their patient and found the mass to consist of normal hepatic tissue

2 Misplaced liver tissue Isolated accessory lobes or accessory livers have been found attached to the liver by a mesentery Isolated nodules of liver tissue have been observed in the suspensory ligaments and engrafted on other organs Liver tissue has been found in the following organs (1) suprarenal gland (2) gall bladder (3) spleen and (4) scattered in the peritoneum These accessory livers contain all the elements of a normal liver cords of liver cells sinusoids Kupffer cells and bile ducts Heid and von Haam demonstrated nerve cells in the heterotopic liver tissue on the surface of the spleen

Rotation of the entire liver on its vertical axis and rotation to assume a vertical position in the abdomen has been described Loss of the

ligamentous attachments may result in the liver lying nearly free in the abdominal cavity

B Liver of Normal Form but Misplaced

Absence or defect in the diaphragm may result in displacement of the liver into pleural cavity Displacement of liver into the left pleural cavity is much more common than displacement into the right pleural cavity This is due to the greater frequency of defects in the left leaf of the diaphragm Defects in the right diaphragm are usually smaller and allow for only partial displacement of the liver Displacement of the liver into the left pleural cavity with right diaphragmatic defects have been described presumably the liver is displaced by pressure of the viscera from the right side Displacement of the liver into the pleural cavity is a serious anomaly since it interferes with the function of the individual however it is not incompatible with longevity

Displacement of a portion of the liver into an amniotic hernia has been encountered at birth Resection of a portion of the liver has been resorted to in order to close the defect in the abdominal wall

Aberrant Hepatic Ducts

Aberrant hepatic ducts have been found in the fibrous attachments of the liver and incised accidentally during a surgical procedure (Rapant & Hromada 1950) This accidental incision may result in troublesome leakage of bile They are most frequently found in the various ligaments of the liver the round ligament the left and right lateral ligaments the hepatogastric ligaments They may also be found in the grooves adjacent to the gall bladder duodenum or esophagus They are of interest not only because of their accidental injury but also because they may become markedly dilated in case of extrahepatic biliary obstruction

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Anatomy of the Major Vessels of the Liver, Aneurism of Hepatic Artery, Occlusion of Hepatic Veins

THE economic importance of a geographic area is revealed by its transportation facilities The unique and important position of the liver in the body economy is emphasized by the abundance and the unusual features of its blood supply It has been estimated that about one quarter of the entire cardiac output passes through the liver each minute (Bradley) This gives the liver an opportunity to exert a controlling influence on blood volume and circulatory dynamics The other unusual feature is that the liver receives blood from a venous as well as an arterial source the portal vein and hepatic artery

Anatomy of the Major Vessels

Hepatic Artery

The hepatic artery is one of the three branches of the celiac artery which arises from the aorta in the region of the renal arteries The

other two branches of the celiac artery are the left gastric and splenic (lienal) artery In the adult the hepatic artery is smaller than the splenic but larger than the left gastric but in the fetus it is the largest of the three The hepatic artery lies next to the common duct and portal vein as it ascends into the porta hepatica The duct lies to the right of the artery and the vein behind The hepatic artery divides into two main branches—the right and left branch—supplying the corresponding lobes of the liver The other branches of the hepatic artery are

1 Right gastric
2 Gastroduodenal
   a Right gastroepiploic
   b Superior pancreatico duodenal
3 Cystic

The level at which these vessels arise from the hepatic artery is important in regard to surgical ligation of the main hepatic artery The right gastric artery is the most proximal branch slightly distal to it is the origin of the gastroduodenal artery which is the largest branch of the hepatic artery The cystic artery is the smallest and most distal branch and usually arises from the right hepatic artery

Portal Vein and Its Tributaries

The portal vein is about 2 cm in its greatest diameter and 5 5 to 8 cm in length from its point of origin at the junction of the splenic and superior mesenteric veins to its bifurcation into right and left branch (Gilfillan) (Figs 60 and 61) The inferior mesenteric vein usually (85% of cases) empties into the splenic vein in a minority of cases (15%) it joins directly with the superior mesenteric The coronary and pyloric veins of the stomach empty directly into the portal vein or into the splenic vein The cystic vein of the gall bladder empties into the portal vein The esophageal plexus empties into an esophageal vein which is a tributary of the coronary vein of the stomach The inferior mesenteric vein receives its blood from the rectum descending and transverse colon while the superior mesenteric vein drains the right side of the colon and small intestine (Fig 6)

Streamlining of the portal venous blood is not a new concept (Copher and Dick 19 8) which has been abundantly substantiated by the observations of Mann and others More recently the physiological bilaterality of the portal blood supply has been demonstrated by

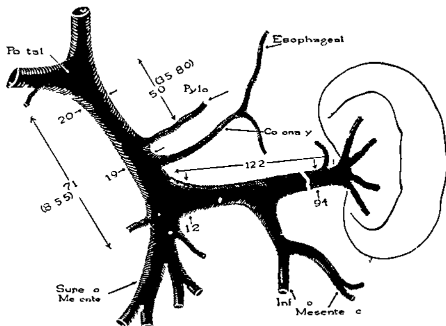


Fig 60 Measu ments in centimeters of the portal vein and its ma n branche (From Gilfil n Arch S rg *61* 449 1950)

Hahn and coworkers by the use of radioactive phosphorus When they injected phosphoric acid containing a radioactive isotope into the splenic vein the accumulation of radioactive phosphorus was much greater in the left side of the liver When the tagged material was injected into the superior mesenteric vein or one of its tributaries the greatest concentration of radioactive pho phorus was found in the right side of the liver

This evidence as well as that deduced previously by the u e of dyes and transillumination of vessels indicates that there is a left and right stream of blood in the portal vein which do not become mixed and enter the left and right branch of the portal vein and the corresponding sides of the liver This is a most important concept for pathological a well as clinical orientation since toxins tumors and nutrients arising from a given organ or portion of the gastrointestinal tract will more likely reach one side of the liver than the other Thus the stomach the spleen and lower colon contribute to the left stream while the mall intestine cecum and ascending colon contribute to the right side of the liver

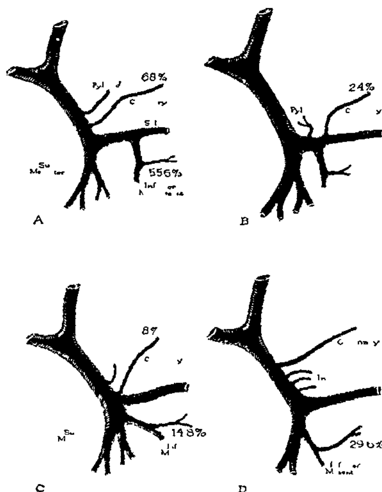


Fig 61 Variat of the morphology of the portal vein (From C Mill Arch S g 61 449 1950)

Proportion of Venous and Arterial Blood Supplied to Liver

The question of the proportion of blood brought to the liver through the arterial and venous channel is an important one This is of interest in the normal subject but becomes of crucial importance in case of interference with or interruption of one of these The old concept that one fourth to one third of the blood supply is arterial and the rest is venous is based on unsound observations and is probably erroneous More reliable observations seem to indicate that the relative proportion of the blood from the two systems shows a wide variation according to circumstances The total blood flow to the liver depends on cardiac output but either vessel may carry as much as 90% of the total blood according to Soskin and coworkers and according to Grindley and associates The hepatic artery can carry from 11 to 83% of the blood entering the liver It has been suggested that as the blood pressure falls the dependence on the arterial supply rises One may safely conjecture that a partial obstruction of either results in a diminution of supply from it and a greater demand on its unmolested partner

It may be assumed that oxygen is supplied exclusively by the arterial route This however is not true and depends a great deal on the species of animal Some animals rely more on the portal venous blood for the oxygen supply to the liver The varying response of different animals to occlusion of these two sources of blood may depend on the varying source of the oxygen supply (p 337)

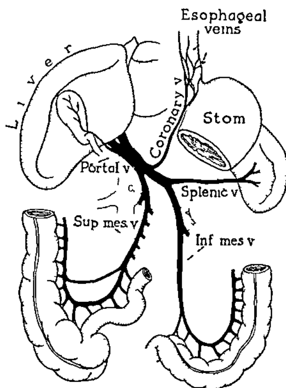


Fig 6 Diagrammatic scheme of portal vein taries and important anatomical relationships

The Hepatic Veins

While the blood supply to the liver is dual in origin the blood leaves the liver through one channel—the hepatic veins The central lobular veins which receive the blood from the portal vein and hepatic artery in turn contribute to the formation of the hepatic veins The hepatic veins are usually three in number originate in the substance of the liver and empty into the inferior vena cava which lies in a hepatic groove The hepatic veins have no valves but there is evidence from experiments on the dog that the hepatic veins have a powerful contractile mechanism which controls the flow of blood through the liver by sphincteric action It is also suggested by the hepatic blood flow studies of Bradley that the other vascular components of the liver may be subject to vasodilatation and vasoconstriction resulting in alteration of hepatic blood flow

Aneurysm of the Hepatic Artery

Incidence

Aneurysms of hepatic artery are rare since only 87 cases were found in the literature up to 1950 (Grant et al) This condition is nevertheless of importance since it is productive of signs and symptoms that may be confused with more common hepatic diseases and because newer techniques make it amenable to successful therapy

Age and Sex

The average age of these patients is 38 with a range between 10 and 83 years There is a preponderance of males in a ratio of 3 to 1

cular mass by compressing the common
d cystic ducts produces biliary stasis in
nd other features of extrahepatic biliary
(p 115) Besides the bile necrosis there
ecrosis due to obstruction of the arterial
ly with changes similar to hepatic infarc
2)

urysm

urysms may be intrahepatic or extrahe
atter are about three times more common
e 84 cases had both intra and extrahepatic
The extrahepatic aneurysms may be in
on hepatic artery right branch or left
both branches in decreasing order of fre
he cystic and gastroduodenal arteries have
found involved The aneurysms may be
nd as many as five in one patient have been

urysm

eurysm varies in size from less than a
in diameter to the size of a child s head
hepatic lesions are usually largest but an
ic aneurysm the size of a grapefruit has
in the literature

erial les on may be a true or false aneu
smaller ones are usually true aneurysms
ation of the weakened vascular wall The
s are false aneurysms consisting of hema
ned in a partially ruptured aneurysm

c Features

s in the vessel wall are usually indicative
cific inflammation Specific changes indica
philis are found in some Atherosclerotic
ith or without calcification are found in
fourth of patients Evidence of healing by
n tissue as well as thrombosis and hemor
detected

aneurysms elsewhere the three im
tiologic factors are (1) infection (2)
erosis and (3) trauma in this order of
) Infection alone accounts for about
he cases (Malloy and Jason) However
eurysms of the aorta syphilis is rela
ncommon while the acute infections
ost frequent etiologic factors Thus in
where the etiologic factor was infection
n had syphilis while the other 34 had
s such as pneumonia empyema

osteomyelitis liver abscess typhoid cholecys titis and other infections Tuberculosis was present in one patient (Malloy and Jason) It is likely that arteriosclerosis or some degenerative arterial condition may precede even in those on an infectious basis This may be surmised from the age distribution of the patients Hepatic artery aneurysms are most common in advanced age when arteriosclerosis prevails rather than in childhood when infectious diseases are most frequent

Traumatic aneurysms are chiefly intrahepatic while the others are extrahepatic The extrahepatic aneurysms are most important in as much as they are productive of symptoms and attended by the most serious complications Cholelithiasis may have a dual role in the etiology both as trauma and infection Trauma may also be applied externally or follow surgery

Clinical Features

The clinical triad that should make one think of hepatic artery aneurysm is (1) pain ( ) gastrointestinal hemorrhage and (3) jaundice When one adds to this a palpable pulsating mass that has a systolic bruit the diagnosis should be complete Because of its rarity it is seldom considered and therefore the diagnosis is usually made at autopsy and rarely at surgery

The pain (80%) is usually in the right upper quadrant or epigastrium It may be aching throbbing or colicky in quality and aggravated by exertion Hemorrhage (63%) may be due to erosion into the extrahepatic bile ducts which is most common or into duodenum or other parts of the intestine This appears clinically as hematemesis or melena When bleeding occurs into the bile ducts it is usually preceded by jaundice and therefore may be confused with neoplasms producing biliary obstruction The hemorrhage is brisker than that seen in neoplasms When hemorrhage occurs into the intestinal tract the more likely confusion is with peptic ulceration The other symptoms and x rays may help to clarify the diagnosis

The jaundice is due to obstruction of the common or hepatic ducts by the pulsating mass or to concomitant cholelithiasis The jaundice

may become marked and accompanied by pruritus One would expect the jaundice to fluctuate especially in the early stages and may conceivably subside after hemorrhage

Fever was observed in the two cases reported by Grant and coworkers and may be due to the pre existing infection the inflammatory process in the aneurysm or the cholangitis resulting from compression of common duct

Hepatic enlargement may be occasionally observed The finding of a pulsating extra hepatic mass although uncommon is of course the most diagnostic finding although trans mitted pulsation from a solid tumor straddling an artery may result in error A palpable thrill and systolic bruit may further aid the diagnosis

Laboratory Findings

Liver function tests indicative of hepato cellular damage are usually normal unless infarction has resulted in considerable hepatic necrosis The flocculation tests are therefore likely to be normal The serum bilirubin is elevated and is chiefly of the prompt reacting type The stool and urine pigments are com patible with posthepatic jaundice

The blood may show an anemia if bleeding has taken place and leucocytosis with pre ponderance of neutrophiles if infection is the causative factor Stools may be grossly bloody tarry or show the presence of occult blood de pending on the size and speed of the hemor rhage

X ray may show pressure against duodenum or lesser curvature of stomach If the duodenal bulb is deformed by extrinsic pressure con fusion with duodenal ulcer is likely because of the history of hemorrhage Calcification in the aneurysm may aid in the roentgenographic diagnosis

Diagnosis and Differential Diagnosis

Theoretically the diagnosis should be strongly entertained in the presence of right hypochondriac pain jaundice hemorrhage ac companied by a pulsating mass emitting a systolic thrill Practically the diagnosis is frequently missed even at surgery because the condition is seldom considered The diagnosis usually awaits the necropsy

In the presence of jaundice the problem is one of differential diagnosis of this sign and especially the differential diagnosis of post hepatic jaundice If hemorrhage is in the fore ground it must be differentiated from other causes of upper gastrointestinal hemorrhage

Duration and Cause of Death

The duration from onset of symptoms to death may be only a few hours or several months Hemorrhage into the gastrointestinal tract the bile ducts or free peritoneal cavity is usually responsible for the patient s exitus

Treatment

Treatment is poor as it is in all aneurysms of arteries leading to vital organs Three ap proaches are possible which with improved surgical technique and better understanding of the physiology and circulation of liver may become practical These include (1) ligation of hepatic artery (2) reconstruction of hepatic artery (3) wrapping of cellophane around aneurysm or artery proximal to aneurysm and (4) arteriovenous anastomosis between hepatic artery proximal to aneurysm and portal vein These various therapeutic approaches are dis cussed in some detail by Grant and coworkers

Ligation of the hepatic artery for aneurysm has been successful in three cases which were reported in the German literature If the artery is ligated proximally to its major branches the right gastric and gastroduodenal arteries circu lation may continue through anastomosis with the left gastric and superior mesenteric Liga tion distally to this area may become safe after the development of new collateral circulation because of the gradual occlusion of the artery or in the presence of anomalous arteries With the institution of antibiotic therapy ligation of the hepatic artery may become less hazardous (Markowitz and coworkers) (p 332)

Reconstruction of the hepatic artery by vein or artificial graft after excision of the aneurysm would be ideal if the technique were perfected Wrapping of cellophane or other plastic around the aneurysm may prevent rupture of the vessel stimulate fibrosis and collateral circula tion The surgical production of arteriovenous fistula would help to assure oxygen supply to

the liver and relieve the pressure from the weak artery but the increased portal pressure thus created would lead to the danger of hemorrhage from esophageal varices and thus replace one evil by another (p 338)

Occlusion of the Hepatic Veins (Chiari's Disease Budd Chiari Disease)

Occlusion or thrombosis of the hepatic veins is a rare disease first referred to by Budd a century ago and described by Chiari over 50 years ago and hence carries the names of the original observers

Incidence

The rarity of the disease is indicated by the fact that approximately 115 cases were found in the entire literature up to 1952 (Little and Montgomery) Kelsey and Comfort found only 20 cases in 29 years at the Mayo Clinic but in only four cases did it influence the clinical picture and in the remaining it was an incidental pathological finding Only two cases have been reported in the Scandinavian countries up to 1950 (Salversen and Torgersen) and in the American literature most of the reports consist of single cases

Pathogenesis

Occlusion of the hepatic veins may occur because of primary disease in these veins which is rare (the term *disease* is used) or secondary to disease of the liver or elsewhere in the body (the term *syndrome* is used) The following classification is useful

A Primary
- 1 Primary phlebitis (obliterative phlebitis)
- 2 Primary thrombosis
- 3 Retardation of blood flow in hepatic veins
- 4 Mechanical injury of veins by pull of liver
- 5 Congenital stricture

B Secondary
- 1 Hepatic causes
  - a Inflammatory
  - b Neoplastic
  - c Cirrhotic
- 2 Extrahepatic
  - a Trauma
  - b Scars
  - c Perihepatitis
  - d Extension of thrombus from inferior vena cava
  - e Constrictive pericarditis
  - f Polycythemia vera
  - g Thrombophlebitis migrans
  - h Malignant or infectious emboli
  - i Toxin—Senecio poisoning

The primary causes for hepatic vein occlusion are fortunately less common and most of them can not be prevented Syphilis has been suspected as a cause for the phlebitis but recent evidence does not substantiate this A primary thrombosis without changes in the clotting mechanism of the blood is difficult to conceive However a Scandinavian report deals with an unusual case of this disease in which (1) thrombosis occurred in the sublobular veins and smaller veins (2) there was a lack of involvement of main branches of hepatic veins (3) there was an absence of inflammation in the walls of involved veins and (4) there was an absence of other factors responsible for thrombosis such as polycythemia It was suggested that the cause of the thrombosis may be a primary disorder in clotting mechanism of the blood leaving the liver (Salvesen and Torgersen)

Hepatic causes include inflammatory processes such as syphilitic and tuberculous granulomas hydatid cysts and pyogenic abscess Hepatic neoplasms especially malignant hepatomas have a tendency to invade and occlude veins (Chapter 19) In cirrhosis very rarely, the vascular injury may extend to the larger veins and eventually to the hepatic veins

Among the extrahepatic causes diseases that are accompanied by acceleration of clotting mechanism such as polycythemia vera and migrating thrombophlebitis as well as neoplastic invasion of vena cava are most frequently responsible for hepatic vein occlusion Other blood dyscrasias such as leukemia may become complicated by hepatic vein thrombosis Plough and Bevans reported a case of Chiari's disease occurring in a young man with thrombophlebitis of the leg This was followed by caval thrombosis and obstruction of hepatic

veins One wonders whether an embolism may have played a part in this case Hepatic vein thrombosis has also occurred secondary to nephrosis (Dodd et al) Generalized vascular disease is an important etiologic factor Onset of this illness in relation to pregnancy has also been noted

A toxin which is present in certain species of Senecio (ragwort weed) and recognized as a cause of poisoning in horses and cattle has been reported as a cause of Chiari s syndrome in twelve patients in Cape Town South Africa Autopsy studies were done on six (Selzer and Parker 1951)

Trauma to the chest may result in injury and thrombosis in the vena cava resulting in obstruction of the hepatic veins This is a rare etiologic factor but one such case was recently reported (Little and Montgomery)

Pathology

The vascular lesion varies according to the exact cause of the occlusion and the duration of the occlusion before death The involvement varies also as to the exact localization Only one or all of the main hepatic veins may be involved or there may be involvement of the vena cava at the ostia of the hepatic veins In an isolated case the large veins may be free of thrombus but the sublobular veins are involved (Salversen and Torgersen) The vessel wall may show evidence of inflammation (phlebitis) and the clot may consist of purulent or malignant material depending on the cause of the obstruction The clot may be organized if ancient or soft and friable if recent The vein may be fibrosed and turned into a fibrous cord

Hepatic changes are seen throughout the organ if all the veins are occluded or may be confined to one lobe if only one of the veins is thrombosed The character of the changes depends on the duration of the occlusion and upon its completeness In animal experiments even partial obstruction of the hepatic veins results in centrilobular necrosis which is followed by fibrosis around the central veins The changes are similar in man

Grossly the liver is enlarged and congested If the occlusion does not involve all the veins wedge shaped areas of congestion are seen corresponding to the vein occluded Microscopically the central veins are distended or thrombosed The engorgement which also involves the sinusoids is most marked in the early stages This is accompanied by centrolobular necrosis In the more chronic disease fibrosis replaces the necrosis and the organ may be reduced in size Regeneration may give the organ a nodular appearance and microscopically scarring and newly formed hyperplastic parenchymal are seen side by side A mixture of old and r lesions may be seen in the same liver if rep small thromboses have taken place

Primary carcinoma of liver has been report developing secondary to the cirrhotic proce hepatic vein occlusion (Hutchison and Simp but is more likely to be the primary lesion thrombus may extend into the portal vein and r in infarction of the intestines The spleen s severe venous congestion and is enlarged

Ascites is a constant feature (See p 3 9)

Clinical Features

Age The youngest patient cited by Tho son was an infant of 17 months the oldest 70 years of age Most patients are from 40 years old

Sex It occurs almost equally in both se although of 88 patients in whom sex is corded 50 were males and 38 females

Sypmtoms and Findings

Asymptomatic form Thrombosis of hepatic veins is regarded as such a catastro illness that it may be surprising to learn t 16 of the 20 cases from the Mayo Clinic asymptomatic and were found incidentally autopsy In such cases the thrombosis have existed for a long time and became canalized or developed ante mortem and over hadowed by the primary disease or thrombosis was not extensive

Symptomatic form The disease may run acute rapidly downhill course ending w death in from one to four days or the cou may be more chronic lasting for several we to several months

The disease is usually ushered in with e gastric or right hypochondriac *pain* varying character and intensity The pain may be m at first bordering on discomfort or a ense pressure, and rapidly increase to severe cram ing pain Minor attacks of pain over a period years have been reported which may be due minor thromboses Occasionally the pain m radiate to the back or to the lower abdom The pain is undoubtedly due to stretch ng liver capsule due to engorgement The rapid developing portal hypertension and hen mesenteric vein hypertension may result

engorgement of the intestines and pain from this source.

A shock-like picture has been described in the acute occlusions and this may be accompanied by cyanosis. Dyspnea may be present due to the massive ascites or pleural effusion which is a rare finding. Vomiting during the initial episode in about one fourth of the patients has also been observed.

While fever has been recorded in many cases in the literature it may not be attributable primarily to the venous thrombosis since the antecedent disease is frequently of a febrile nature.

Ascites is almost invariable. It develops rapidly and is massive. The ascites may be hemorrhagic and recur rapidly after paracenthesis. In keeping with the experimental studies of Bollman who invariably produced ascites by occluding the inferior vena cava above the hepatic veins this finding should be present without exception in this disease (Chapter 54). The absence of ascites in a rare case may be explained on the basis of (1) incomplete occlusion, ( ) gradual occlusion with development of collateral circulation and (3) chronic occlusion with recanalization.

Jaundice is an inconspicuous feature in this disease. When it occurs it is mild. The relative mildness of the jaundice may be explained on the basis of the rapid death which does not allow sufficient time for jaundice to occur. Since the venous return from the liver is occluded the bilirubin accumulating in the liver may not gain access to the general circulation.

Rapid hepatic enlargement is a striking feature but this may be difficult to demonstrate because of the massive ascites. Its detection may have to await paracenthesis. However if palpation is unsuccessful the enlarged liver may be balloted in the ascitic fluid. The enlargement may extend 6 to 8 cm below the costal margin and tenderness is elicited on palpation. At first the organ is soft but if the patient survives the liver becomes firmer and smaller due to development of fibrous tissue. Irregularities or nodules may be palpable if the primary disease is a neoplasm or cyst.

Splenic enlargement is not as frequent nor as conspicuous as hepatic enlargement. Usually the enlargement is only slight about - cm below the costal margin but larger spleens have been described.

Nature's attempt to replace the thrombosed vein by collateral circulation becomes apparent in the development of engorged veins over the lower thorax and upper abdomen. The anastomosis between superior epigastric medial xiphoid and internal mammary vein results in dilatation of veins around the xiphoid cartilage (Thompson). True caput Medusae are uncommon. In general the prominence and size of the collateral circulation is a function of the chronicity of the disease. It may take several weeks for definite collateral circulation to develop; therefore unless the patient survives that long or the occlusion is gradual in onset no venous engorgement may be detectable.

Edema of legs is a frequent occurrence but may be mild unless the thrombosis involves the inferior vena cava. The edema may result from other factors besides venous occlusion such as hypoproteinemia and sodium retention.

Extension of thrombosis to the portal vein may result in esophageal varices. Hemorrhage from these may conclude the final chapter of the disease. When the occlusion extends to the mesenteric vein infarction of the intestine may produce violent abdominal pain and bloody diarrhea. Diarrhea has been described without obvious mesenteric thrombosis.

Disturbances of consciousness may occur and be related to hepatic failure. However physical findings suggestive of involvement of corpus striatum such as mask-like facies, monotonous speech and tremors have been reported. Changes in the brain at postmortem are cited by Thompson.

Pulmonary emboli may apparently develop from thrombi breaking off and traveling up the ascending vena cava. One of Kelsey and Comfort's cases showed this complication.

Patients may develop marked acidosis but this is probably on an hepatic rather than renal basis. Altschule and White reported one case ending in uremia. The thrombosis usually does not involve the renal veins. However in the cases reported by Dodd and his associates and Plough and Bevans the renal veins were involved and azotemia developed.

Clinical Features—Summary

Age
- 17 months to 70 years
- 20 to 40 years most common

Sex
- Equal distribution

Symptoms
- Asymptomatic form exists
- Symptomatic form
  - Acute with death in one to four days
  - Chronic with survival for years
- Pain
  - Site epigastric or right hypochondrium
  - Character
    - mild at first
    - very severe eventually
    - cramping
    - minor attacks of pain over years in chronic form
  - Radiation back lower abdomen caused by
    - stretching of Glisson s capsule
    - intestinal passive hyperemia

Physical findings
- Vomiting in one fourth of patients
- Shock, Cyanosis } more common in acute form
- Dyspnea due to pleural effusion or ascites
- Fever
- Jaundice—inconspicuous or absent
- Ascites—massive—develops rapidly and may be hemorrhagic
- Hepatomegaly
  - rapid enlargement
  - tenderness
  - soft at first
  - firm later
- Splenomegaly—slight and inconspicuous
- Superficial veins
  - lower thorax
  - upper abdomen around xiphoid cartilage
  - Caput Medusae rare
  - several weeks to develop
- Edema due to
  - vena caval involvement
  - hypoproteinemia
  - sodium retention
- Esophageal varices with hemorrhage from portal vein involvement
- Signs of mesenteric vein thrombosis
- Central nervous system signs
  - hepatic coma and pre coma
  - occasionally signs of corpus striatum involvement
- Complications
  - pulmonary emboli
  - uremia from involvement of renal veins

Laboratory Tests

Liver function tests show considerable abnormality Bromsulphalein retention is reported by Davis and coworkers and Kelsey and Comfort Decreased prothrombin values and elevated alkaline phosphatase have been observed Decrease of both the total and esterified cholesterol have been noted Hypoproteinemia and reversal of the albumin/globulin ratio can occur The serum bilirubin is only slightly elevated and the urine shows urobilinogen and some bilirubin in the jaundiced patients Macrocytosis may be attributable to hepatic damage (Kelsey and Comfort)

Other laboratory tests may mirror the primary disease responsible for the hepatic vein thrombosis Thus polycythemia thrombocytosis leucocytosis leukemic blood picture or anemia may be found depending upon the nature of the primary disease Differential diagnosis will be discussed together with the other diseases of the blood vessels

Treatment and Prognosis

The prognosis in the majority of cases is grave death occurring in several days but in a small group the syndrome runs a chronic course and the survival of a patient for 5 years has been reported (Hutchinson and Simpson)

The treatment of the disease may be divided into two categories (1) treatment of the liver injury and (2) reversal of thrombotic phenomenon The first consists of dietary and supportive measures similar to those used in portal cirrhosis Paracenthesis has been condemned by some as resulting in rapid deterioration of patient This condemnation of paracenthesis i

probably unjustifiable, the procedure should be used to remove massive ascites which may produce dyspnea and pain. Mercurial diuretics are even more dangerous in this condition than in portal cirrhosis because of the toxic state of the patient.

Since polycythemia vera is an important cause of thrombosis of hepatic veins, the use of radioactive phosphorus may prevent this serious complication and this agent should be used after the thrombosis occurs. From five to seven millicuries can be administered intravenously or orally, since the oral absorption is quite rapid. The oral route may be prohibitive if vomiting occurs. Dicumarol (dicoumarin) and heparin can be used in the usual manner. Dicumarol has been used successfully in spite of a low plasma prothrombin (27.8%) by Davis and his associates. Because of the liver damage less dicumarol is necessary and the prothrombin time should be watched carefully. The gravity of the situation requires a courageous therapeutic approach, even though it may be risky. Davis and coworkers report the cure of a case with these measures. The patient was followed with serial liver biopsies. Liver biopsy is also fraught with danger because the marked congestion may predispose to hemorrhage.

47 — *Hepatic Infarction, Cruveilhier-Baumgarten Syndrome*

HEPATIC INFARCTION

Incidence

ALL reviewers agree that hepatic infarcts are rare, although the exact incidence varies depending on the definition of the term. Its rarity, as well as the confusion in identification, depends upon the peculiarities of the hepatic circulation as well as other factors involved in the pathogenesis of this entity. 54 cases of infarcts of liver were found in 28 years among 18,230 autopsies at the Mayo Clinic (Woolling et al. 1950). In 1935 Lund and coworkers found only 20 acceptable cases of hepatic infarcts in the literature and reported eight cases, while in the same year and in the same journal Pass found 52 cases of anemic infarction of the liver in the literature and reported two additional cases.

Pathogenesis of Infarction

The generally accepted definition of infarction is an area of necrosis resulting from obstruction of the blood supply. While in most organs this means arterial occlusion, the liver, because of its dual blood supply, can show infarction because of portal venous occlusion. Thus in 37 cases reported from the Mayo Clinic in which a major vessel was occluded, in only ten was the hepatic artery or its branches solely involved, in 11 cases both the hepatic artery and portal vein were involved, portal vein alone in 11 cases, portal and hepatic veins in three cases, while in one all major vessels were involved.

The result of occlusion of the hepatic artery varies in different species and in different members of the same species. Tying the hepatic artery in the dog results in massive necrosis, while in the rat the procedure is unattended by ill effects. Pass reviewed the literature of accidental and therapeutic ligation of the hepatic artery and points out that while in most instances fatal infarction resulted, a few survived without ill effects. The consequences of hepatic artery ligations depends apparently

on (1) the exact site of ligation (2) the collateral circulation (3) the relative amount of oxygen supplied by the hepatic artery and portal vein (4) susceptibility of the liver to infection and (5) unknown factors

Obstruction of the hepatic artery at its origin from the celiac artery may not result in dire consequences because of available collateral circulation however obstruction of the arterial supply close to the liver may end fatally The liver may receive arterial blood from sources other than the hepatic artery and in the dog two small arteries enter the liver around the attachment of the vena cava to the liver and another artery near the entrance of the portal vein (Bollman) Similar collateral and accessory arteries may be available in man

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4 The ligation of a branch of the hepatic artery is fraught with danger especially in patients with cardiac disease

Not all species of animals rely equally on the arterial oxygen supply to the liver Some animals get more of the oxygen from the portal vein than from the hepatic artery (McMichael) In these animals obstruction of the hepatic artery does not result in marked anoxia with its serious consequences

Role of Antibiotics

One of the most interesting and far reaching recent observations in this field was made by Markowitz and Rappaport They found that the fatal liver necrosis produced in dogs by ligation of the hepatic artery can be prevented by injection of penicillin When the penicillin injection was continued for ten days the animals survived indefinitely Markowitz theorizes that the dog s liver normally harbors spores of anaerobic bacteria These begin to multiply when the oxygen supply is reduced by ligation of the hepatic artery and the animal dies from gas gangrene of the liver ' Bacilli similar to bacillus Welchi have been demonstrated The penicillin inhibits the multiplication of these organisms and eventually collateral circulation develops to bring oxygen to the anoxic liver and the animal survives without further penicillin Other animals that do not succumb to occlusion of the hepatic artery may not harbor these organisms or be resistant to them Whether the growth of anaerobic bacteria is responsible for the pathologic process in human infarction or whether it is preventable by antibiotics is uncertain In the series of cases reported by Woolling and coworkers five showed gas formation and bacteria in one case compatible with that of bacillus Welchi were found Cultures of liver tissue from individuals without infections or liver disease have been found to be sterile (Sborov et al 1952)

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Microscopic The histologic appearance in all is similar There is a central zone of necrosis involving the entire lobule The lobular pattern may be preserved and the outline of the individual cells may be detectable The sinusoids are empty or contain ghost red cells Adjacent to the central area of necrosis there may be an area of partial necrosis while the cells around the portal triads are well preserved Much acidophilic material may be present in the area of partial necrosis Distally to the zone of partial necrosis there is a zone of reaction which consists of inflammatory cells polymorphonuclear leucocytes macrophages and lymphocytes

In the red (hemorrhagic) infarcts much hemoglobin and hemoglobin like material may be seen The branch of the hepatic artery leading to the infarct may be completely occluded by fibrin and masses of platelets leucocytes and erythrocytes

Bacte a may be found n the necrot c a ea an l some of these may ha e the mo pl olog cal characte st cs of the Welch bac llus

Patholog c ev dence of the assoc ated d sease s foun l the exact nature of wh ch depends on the type of antecedent d sease I e te t s nodosa ma nvolve the hepat c a tery subac te bacter al endo card t s m y be respons ble fo an r er al embo sm or a gastro ntest nal cond t on may be found wh ch s respons ble for the v c lar occlus n

E ology

Assoc a ed d eases The t o large gr p of d sea es tl at are respons l le f r hepat c arter al occl s on are d ea es of the card ovascular and gastro nte t nal tract Pass a al ed the et o log c *facto s n* 52 ca e of hep t c nf rcts an l found the follow ng d str b t on

Emb m o h p c a ery	
a b e b end a d	3
b m l thromb	4
c p ad al mb m	
d h mb n an a u m	
To al Emb l	2
Peri e od f b ch of h p c a r	2
3 Th omb of h pa a h e n a m	6
4 End e of h pa c a	
5 H pepla a of h p v	

Th s d tr but on of et olog c d sea es d ffers a good deal from tho e reported by Woolling and coworker They found d seases of the ga tro nte nal tract respon ble n 31 of tl e 54 ca es and in only 13 cases were card ovascu lar d ea es re pon ble 17 of tl e ga tro tes nal g o p had neopla ms and 9 had undergone su ge w thout clea cut tra na f the hepat artery (see Table 54) Only one case each of l pus erythen a o u and per arter t nodosa were fo nd Traun a to l ver sub tance dur ng operat ons or du ng del ve y n nfant may res lt n nfarct on Se ere external tra ma ma result n ntarct o of tl e l er

Age and sex Ne ther age nor sex seems to be pred po ng factor n hepat c nfarcts In the Mayo Cl n c e e the e were o female and 34 male who e age var ed between one day an l 78 ears The pat ent n I nd and co workers er es var ed n age between 3 and 64 years

TABLE 4

C fi n of he P ma D ea e A soc d w h Infa of he I e

P m y D	C
Ca n D	
D e of he g b dd d b ee	8
Ca n ma	7
Ca l one	6
Infl mma n	5
D f he S oma h P n nd In n	
Neop a m	0
I fl mm n	
Ca d a D a	3
D a f h Sp n	
N n	7
To a	54

F m W ng *Bagg n* d W *G* o r g 4 9 9

Cl ntcal p ct re If extens ve nfarct on occu the cl n cal p cture may be fulm nat ng an l rap dly do nh ll Pa n o er the l ver area may be e ere Jaund ce s frequently p esent but s not marked Tenderness of the liver ith muscle g ard ng comn only seen The p cture n ay a sume the character st cs of a hepato renal syndro e w th l gh fever con a para l t c leus ol gur a and azotem a Death may occur n several da s It s po s ble that the dead l ver t s e ma prec p tate the ent re s ndrome A mall amount (about 5 gm) of de l l ver t s e n the per toneal cav ty of a 10 k logram dog result n leath w th n 4 to 48 hours

Labora ory s d es The e stud es sho n a ked bron lphale n retent on m ld hyper b l rub nem a and urea n trogen elevat on I wo ld expect the flocc lat on tests to become abnormal An occas onal low blood urea n trogen can be nte pre ed as lue to severe hepat c nsuffic ency

SYSTE C CO U CAT ONS OF THE PORTAL VEIN

The commun cat ons between the portal and system c (caval) venous c rculat on are of ut m t pract cal mportance n cl n cal n ed c ne The s gn ficance stems fro n the fact that the e con mun cat ons form the collateral c rculat on n po tal ve n obstruct on and anomalou com m cat on produce the Cruve lh er Baum

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Not all species of animals rely equally on the arterial oxygen supply to the liver. Some animals get more of the oxygen from the portal vein than from the hepatic artery (McMichael). In these animals obstruction of the hepatic artery does not result in marked anoxia with its serious consequences

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E olog

Associated d eases The two large gro p of d ea es th t are resp ns ble for hepat c arter al occlus on are d e e of he ca d ovas ul r and ga tro ntes nal tr ct Pass anal zed the et o log c facto s n 5 c es of hepat c nfarct n l found the follo v ng d tr but on

1 Embol m of h p a v	
a uba e b e d a d	
b m al h omb s	4
c pa d x c embo m	
d h mb n n n m	
To l Embo c	
2 n d a of b an h f hep c e	
3 Th omb f h p a y	6
h e n ne m	
4 E da f h p	
H p pa of h p a	

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Age and sex Ne ther age n r sex see ns to be pred po ng facto n l epat nfarcts In the Ma o Cl n c ser e there were o fen ales and 34 males who e ages v r ed between one day and 8 ears The pat ents n l und and co worker ser es ar ed n age between 3 and 64 years

TAB E 54
Cl fi n of h P ma D a A o a d w h I o h L

P m y	*C*
Ga n n D a e	
D ea e f he g l bl dd d b a	8
Ca c ma	7
G	6
Infl mma n	5
D f h S m h I an a d I ne	3
N opla m	o
Infl mm n	
Ca d a D a	3
D a of h Sp n	
M n	7
To al	54

F om W x g Bagg n and We G o e e g 7 479 9

Cl nical pict re If extens ve nfarct on occurs the cl n al p cture may be fulm nat ng and rap dl do vnh ll Pa n over the l ver area n ay be se ere Jau d ce frequently present but s not marke l Tenderness of the l ver w th m scle guard ng is comn only seen The p cture n ay as ume tl e character st cs of a hepato renal syn lrome v th h gh fever coma para lyt c leus ol gur a and azoten a Death may occur n everal days It s po s ble that the lead l er t ue may prec p tate the ent re syndrome A small amount (al out 5 gm) of dead l ver t e n the per toneal cav ty of a 10 k logram dog results n death w th n 24 to 48 ho rs

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Bacteria may be found in the necrotic area and some of these may have the morphological characteristics of the Welchi bacillus

Pathologic evidence of the associated disease is found the exact nature of which depends on the type of antecedent disease Periarteritis nodosa may involve the hepatic artery subacute bacterial endocarditis may be responsible for an arterial embolism or a gastrointestinal condition may be found which is responsible for the vascular occlusion

Etiology

Associated diseases The two large groups of diseases that are responsible for hepatic arterial occlusion are diseases of the cardiovascular and gastrointestinal tract Pass analyzed the etiologic factors in 5[illegible] cases of hepatic infarcts and found the following distribution

1 Embolism of hepatic artery	
a subacute bacterial endocarditis	13
b mural thrombi	4
c paradoxical embolism	
d thrombosis in aneurysm	
Total Emboli	21
2 Periarteritis nodosa of branches of hepatic artery	
3 Thrombosis of hepatic artery thrombi and aneurysms	6
4 Endarteritis of hepatic artery	
5 Hypoplasia of hepatic artery	1

This distribution of etiologic diseases differs a good deal from those reported by Woolling and coworkers They found diseases of the gastrointestinal tract responsible in 31 of the 54 cases and in only 13 cases were cardiovascular diseases responsible 17 of the gastrointestinal group had neoplasms and 29 had undergone surgery without clear cut trauma of the hepatic artery (see Table 54) Only one case each of lupus erythematosus and periarteritis nodosa were found Trauma to liver substance during operations or during delivery in infants may result in infarction Severe external trauma may result in infarction of the liver

Age and sex Neither age nor sex seems to be predisposing factors in hepatic infarcts In the Mayo Clinic series there were 20 females and 34 males whose ages varied between one day and 75 years The patients in Lund and coworkers series varied in age between 3 and 64 years

TABLE 54

Classification of the Primary Diseases Associated with Infarcts of the Liver

Primary Disease	Cases	
Gastrointestinal Disease		
Diseases of the gall bladder and biliary tree	18	
Carcinoma		7
Gall stones		6
Inflammation		5
Diseases of the Stomach Pancreas and Intestine	13	
Neoplasm		10
Inflammation		3
Cardiovascular Diseases	13	
Diseases of the Spleen	3	
Miscellaneous	7	
Total	54	

From Woolling Bergen et al Wr Gastroenterology [illegible] 479 19[illegible]

Clinical picture If extensive infarction occurs the clinical picture may be fulminating and rapidly downhill Pain over the liver area may be severe Jaundice is frequently present but is not marked Tenderness of the liver with muscle guarding is commonly seen The picture may assume the characteristics of a hepatorenal syndrome with high fever coma paralytic ileus oliguria and azotemia Death may occur in several days It is possible that the dead liver tissue may precipitate the entire syndrome A small amount (about 5 gm) of dead liver tissue in the peritoneal cavity of a 10 kilogram dog results in death within 24 to 48 hours

Laboratory studies These studies show marked bromsulphalein retention mild hyperbilirubinemia and urea nitrogen elevation I would expect the flocculation tests to become abnormal An occasional low blood urea nitrogen can be interpreted as due to severe hepatic insufficiency

SYSTEMIC COMMUNICATIONS OF THE PORTAL VEIN

The communications between the portal and systemic (caval) venous circulation are of utmost practical importance in clinical medicine The significance stems from the fact that these communications form the collateral circulation in portal vein obstruction and anomalous communications produce the Cruveilhier Baum

garten disease Edwards in a remarkable paper brought together much of the available information on this subject and demonstrated these communications roentgenographically by injecting radiopaque material into the femoral veins

The existence of these communications has been known to anatomists since the observations by Ruysch in 1738 but there has been a sharp revival of interest in this subject Edwards classified porta systemic communications as follows

I Abnormal termination of major portal component

II Normal porta systemic communications

  A Deep pathways

    1 Retroperitoneal

    2 Rectal

    3 Diaphragmatic

    4 Esophageal

  B Anterior parietal pathways

The abnormal termination of a major tributary is very rare and actually consists of a spontaneous porta caval shunt where a major portion of the portal blood is diverted to a systemic venous channel Edwards cites two cases of the termination of the portal vein in the inferior vena cava near the renal veins a spontaneous porta caval shunt One of these patients died accidentally at the age of 13

Normal Porta Systemic Venous *Communication*

The normal porta systemic communications consist of numerous fine vessels in the posterior parietes of the thorax abdomen and pelvis Thus in the region of the esophagus the following veins served as shunts between the two systems (1) posterior mediastinal (2) intercostal (3) azygos (4) superior phrenic (5) pericardiophrenic and (6) internal mammary In the region of the spleen and stomach (1) the inferior phrenic (2) the left suprarenal (3) left renal and hemiazygos serve as shunts Around the rectum (1) the middle and inferior hemorrhoidal (-) the sacral veins of bladder *and internal genitalia* participate in the porta caval shunts

Communication between the portal system and the anterior parietes occurs through the umbilical or Sappey s parumbilical vein which connects with the inferior epigastric veins

In the injection experiments conducted by Edwards filling of the portal vein occurred through the normal undilated venous communications The anterior parietal veins showed slight filling only in a patient with cirrhosis in whom many fine vessels around the falciform ligament communicated with the superior and inferior deep epigastric veins as well as with superficial abdominal veins

Collateral Circulation in Portal Obstruction

The deep parietal anastomoses which are available normally are more frequently utilized for collateral circulation in intrahepatic portal obstruction (cirrhosis) than the anterior parietal veins It is a common clinical experience that esophageal varices are encountered more frequently in cirrhosis than markedly dilated abdominal veins Indeed dilated esophageal veins are seen in the absence of any dilatation of superficial abdominal veins In extrahepatic portal obstruction developing slowly over a long period of time the deep posterior parietal channels can enlarge to a remarkable degree and take over the flow of blood without the production of symptoms while sudden occlusion of the vein results in intestinal infarction

The greater availability of the posterior parietal communications is supported by the clinical observations that esophageal varices are more common in portal cirrhosis than dilated anterior abdominal veins in ascite the failure of the posterior communications results in the greater frequency of subcutaneous venous enlargement The anterior parietal veins (periumbilical) are more frequently *utilized in portal* than in caval obstruction and the connection between them and the portal vein is effected through the umbilical or parumbilical vein (Vein of Sappey) These veins are valveless while the parietal vessels contain valves However since the periumbilical veins extend in a centrifugal manner *from the umbilicus* to th veins above and below no obstacle to the flow of blood is presented

In general the availability of a vein for

collateral circulation depends on (1) its course (2) the direction of the valves and (3) the size of stoma Vessels running parallel to occluded vessel are generally available for collateral purposes If the valves point in the wrong direction they may be a hindrance to the flow of blood however when the vessel dilates the valves become incompetent and they no longer hinder the flow of blood If a large vessel ends in fine communicating veins it is markedly decreased in usefulness because the fine arborization reduces the amount of blood it can carry

Cruveilhier Baumgarten Syndrome—Disease—Cirrhosis

In the embryo the structures that contribute to the formation of the portal vein and vena cava communicate with each other These structures are the vitelline vein which goes into the development of the portal vein and the right subcardinal vein which forms the inferior vena cava The umbilical veins are paired with the vitelline veins in the embryo and the left umbilical vein empties into the left branch of the portal vein and contributes to the sinus formation of the left lobe of the liver After birth and ligation of the umbilical cord the umbilical vein atrophies to form the ligamentum teres within the falciform ligament The upper portion of the umbilical vein may remain patent into adult life to form the Rest Kanal of Baumgarten Normally there is no communication between the remnant of the umbilical vein and the epigastric veins in the abdominal wall

When the increased pressure in the portal vein in portal cirrhosis results in a recanalization of the umbilical or paraumbilical vein (which may represent the right umbilical vein or segments of the vitelline veins) the markedly dilated connection with the epigastric abdominal veins results in a true caput Medusae The eddying currents of blood in these dilated veins or the flow of the current into vessels of abruptly changing calibre results in a hum or murmur This combination of the dilated periumbilical veins the venous hum and portal cirrhosis can be properly referred to as the Cruveilhier Baumgarten syndrome

Cruveilhier Baumgarten disease should be used to designate the condition in which there is a congenital patency of the umbilical vein hypoplasia of the liver dilated periumbilical veins and venous hum In this instance the patency of the umbilical veins is primary atrophy of the liver is secondary and there is little or no cirrhosis Hepatic fibrosis if present is secondary to the atrophy and portal hypoplasia In the syndrome venous dilatation is secondary to the cirrhosis Clinically these two conditions are indistinguishable and their final separation is possible only at autopsy

Historical

This curious clinico pathological condition dates back to 1833 when Pegot described a patient who presented dilated abdominal veins with a caput Medusae and a loud venous murmur at the umbilicus At autopsy a patent umbilical vein a small but grossly normal liver and large spleen were found The description of this case was elaborated by Cruveilhier in 185 In 1908 Baumgarten described a similar case and emphasized the patent umbilical vein and absence of a well developed cirrhosis In 194 Armstrong Adams Tragerman and Townsend reported two cases of their own and in a masterly review clarified the subject and distinguished between the disease and syndrome bearing this name

Definition

The definition and distinction between Cruveilhier Baumgarten disease and syndrome or cirrhosis is given above I will repeat here for emphasis

Cruveilhier Baumgarten disease is etiologically dependent upon a patent umbilical vein which results in hypoplasia of the liver but no cirrhosis or only minor fibrosis splenomegaly dilated abdominal veins caput Medusae and a periumbilical venous hum

Cruveilhier Baumgarten syndrome or cirrhosis is primarily a portal cirrhosis with the development of the anterior abdominal collateral circulation and/or with recanalization of the umbilical vein caput Medusae and venous murmur

Incidence

Armstrong and coworkers found 52 cases in the literature one additional case from the files of the Los Angeles General Hospital and added two of their own Among these 55 cases only five were considered compatible with the disease while the others belonged to the syndrome or could not be classified because of lack of pathological data Two additional cases were reported one each by Celis and coworkers in 1946 and Havens and Gambill in 1952

Pathology

Liver The size of the liver by definition is decreased in the disease but may be small or large in the syndrome Actually in all of the reviewed cases with available data the liver was small in 20 normal in size in two and enlarged in one General atrophy with an occasional minimum fibrosis is present in the disease In 15 cases the liver was described as grossly nodular and cirrhotic Atrophy of one lobe and hypertrophy of a single lobe has also been described The cirrhosis when present has no distinctive features and for this reason Armstrong and coworkers object to the term Cruveilhier Baumgarten cirrhosis

Spleen This organ is enlarged in almost all cases but was described as normal in one case It may be enormous in size weighing 2020 gm in one instance and over 1000 gm in several other cases

Veins The umbilical vein was recorded as patent in 14 instances partially patent in two Obliterated in one and not described in 24 cases The paraumbilical vein was patent in 9 instances The portal vein must have been the seat of increased pressure but no data is available about this point Thrombosis of the portal vein was described twice and hypoplasia of the right branch twice It was recorded as grossly normal in six and not described in 21 Obstruction of hepatic veins was noted in three

Clinical Features

Distribution by age shows a wide range from 2 to 70 years

The sex incidence shows a predilection for males there being 31 males and 13 females This is similar to the sex incidence of portal cirrhosis The Caucasian race is the only race mentioned in all of the reported cases

Etiologic factors mentioned in the syndrome were similar to those mentioned for portal cirrhosis namely alcohol malaria and syphilis Trauma was mentioned in one as possibly resulting in the patency of the umbilical vein

Symptoms are similar to those seen in chronic diffuse liver disease Epigastric and right hypochondriac discomfort and dyspepsia are complained of Abdominal distention was noted by patient in one fourth of the cases Jaundice was seen in 11 patients and is usually not marked Hematemesis and esophageal varices are of the same frequency The hematemesis may be severe enough to cause death Weakness and loss of weight were noted by a few patients In over half of the reviewed cases no symptoms were recorded

Among the physical findings the most important and diagnostic is the venous murmur This was described in 45 cases most commonly situated in the epigastrium next in frequency periumbilical or both epigastric and periumbilical It may occur elsewhere in abdomen The murmur may be soft or harsh it has been described as roaring or having a spinning wheel sound It is frequently continuous and may have a systolic accentuation A palpable thrill is only about half as frequent as a murmur A sound tracing of the murmur was recorded by Havens and Gambill Distended superficial abdominal veins were recorded in 24 patients These are most prominent between the umbilicus and xiphoid over the area of the murmur and thrill They may be enlarged to the size of a finger A true caput Medusae was described in only three patients The liver was palpable in less than half of the cases A definitely enlarged liver is an indication that the case is one of Cruveilhier Baumgarten syndrome rather than disease Atrophy of one lobe and enlargement of the other lobe of the liver has been noted clinically The spleen is more frequently enlarged than the liver and may reach enormous proportions Such may be the case in both the disease and syndrome Ascites was described in only 15 of the collected cases but is usually massive Peripheral edema may accompany the ascites

Laboratory Findings

These may include a blood picture suggestive of hypersplenism ' with an anemia (occasionally macrocytic) leukopenia and thrombocytopenia Evidence of liver dysfunction is to be expected especially in those cases which are secondary to cirrhosis The older cases contain no laboratory data except for elevated serum bilirubin The more recently reported

cases showed a decrease in albumin and elevation of globulin positive flocculation tests and bromsulphalein retention Urobilinogenuria has been described

X ray visualization of a patent umbilical vein and its connection with the portal vein was accomplished by Celis and coworkers They injected a total of 45 cc of 80% Nosylan through a catheter into a dilated abdominal vein Films taken shortly after injection revealed opaque material in the portal venous system

Peritoneoscopy may also be of value in demonstrating a patent umbilical vein but must be performed with caution because of the danger of perforating a large abdominal vein

Prognosis and Treatment

The condition is a serious one with an average age at death of 38 7 years in all of the collected cases However it is not entirely incompatible with longevity since one patient lived to the age of 70 The causes of death are (1) hepatic failure (2) hematemesis and (3) intercurrent infection The treatment is therefore similar to the treatment of cirrhosis Death from bleeding esophageal or gastric varices occurred in only five cases since the abdominal collateral circulation reduces the need for the deeper esophageal anastomosis The treatment of esophageal hemorrhage is described on page 355 Surgical portacaval shunts have not been reported in this syndrome but would be more hazardous to perform and probably not as successful Splenectomy is useless Paracenthesis if performed because of necessity should be done cautiously because of danger of hemorrhage from superficial abdominal veins

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Portal Hypertension, Portal Obstruction

Disturbed dynamics of portal vein circulation are of utmost clinical importance These disturbances are a constant feature in portal cirrhosis and profoundly influence the clinical course of the disease Extrahepatic portal obstruction independent of cirrhosis is also of importance because of its effect on the liver and the spleen and the vulnerability of the collateral circulation

Importance of Portal Venous Blood Supply

It has been pointed out before that the dependence of the liver on its dual blood supply varies according to circumstances The proportion of blood from each source varies in the same animal from time to time The oxygen supplied through the hepatic artery and portal vein varies with the species and with the blood pressure The cat whose liver gets two thirds of its oxygen from the portal vein develops centrolobular degeneration from obstruction of the venous source of blood to one of the lobes The rabbit liver which is entirely dependent on the arterial oxygen supply shows little change from venous occlusion (McMichael) Obstruction of a branch of the portal vein may result in hepatic infarction (p 338 and Fig 63)

An Eck fistula or diversion of the portal blood into the vena cava by portacaval shunt produces a definite effect on the liver Bile salt synthesis which depends on intact parenchymal cells is reduced by this operation (Smith and Whipple) Regeneration of the dog's liver after partial hepatectomy takes place very quickly with restoration to normal after several weeks When the portal blood is shunted away regeneration does not take place at all or very slowly Characteristic atrophic changes occur

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plete and this for two reasons (1) an acute occlusion like a thrombus is likely to occlude the entire lumen while a slowly developing process would allow recanalization (2) a slowly developing occlusion would allow for the building of local collaterals

Finally classification may be evolved around the immediate cau e of the occlusion in the acquired form This may be divided into four large groups infection neoplasm trauma blood dyscrasias The e can in turn be subdivided as follows

I Infection
 A Inside of vein
  Thrombophlebitis pylephlebitis septic emboli
 B Outside of vein
  Abscess causing compression penetrating wall and resulting in phlebitis inflammatory cicatrix
II Neoplasms
 A Inside of vein
  Tumor emboli causing thrombosis
 B Outside of vein
  Compression by benign tumor malignant tumors cysts
III Trauma
 A Penetrating (including surgical)
 B Non penetrating
  1 damaging vein directly
  damage to adjacent tissue with secondary cicatrix formation
IV Blood Dyscrasia (any condition increasing coagulability of blood)
 A Polycythemia vera
 B Thrombocythemia
 C Leukemia

Prehepatic

The portal hypertension that results from a block above the liver that is from an hepatic vein obstruction is dominated by the primary venous obstruction and was di cussed under Chiari s di ease (p 3 7)

Post hepatic (Extrahepatic)

Obstruction to the portal vein itself or one of its major tributaries below the liver is commonly referred to as extrahepatic portal vein block The other terms that have become associated with this group of diseases is Banti s syndrome and congestive splenomegaly The original concept of Banti s disease or splenic anemia which was attributed to a primary idiopathic splenomegaly with anemia leukopenia hemorrhage ending in cirrhosis of liver has been pretty well discarded The term Banti s syndrome referring to portal hypertension due to extrahepatic block and not hepatic cirrhosis but accompanied by splenomegaly and esophageal hemorrhage is still retained in the literature Actually the term should be di carded because it is confused with a disease the existence of which is no longer accepted some cases of portal cirrhosis are carelessly included under this heading and the use of such an all inclusive waste basket term militates against clear and concise thinking

The term congestive splenomegaly coined by Larrabee is better since it points to one of the dominant clinical findings splenomegaly and suggests that it is due to impairment of venous drainage Venous congestion of the spleen occurs in the intrahepatic variety of portal hypertension (cirrho is) as well as in the prehepatic variety (Chiari s disease) The term congestive splenomegaly therefore cannot be properly applied to one of these subgroups In the acquired form of splenic vein obstruction splenomegaly is the earliest as well as the most outstanding sign but in this condition the congestive splenomegaly is not accompanied by hypertension in the portal vein proper

Cavernous Transformation of Portal Vein

While cavernous transformation of portal vein i usually classified as a congenital or development anomaly such may not always be the case The age distribution with a preponderance of patients in older individuals suggests a postnatal development of the lesion In Klemperer 23 cases only one was under 20 years of age while over half (13 patients) were between 40 and 70 The portal vein may develop as a network of numerous small interlacing veins or be replaced by a vascular tumor like mass an angioma or cavernoma It may result from a thrombophlebitic process with sub equent recanalization and the development



Fig 63 Cross section of liver showing area of infarction and thrombosed branch of portal vein The patient was a 56 year-old man who had undergone a gastric resection one week before A hemorrhagic pancreatitis was also present

in the liver after an Eck fistula and it is difficult to keep the animal in good physical condition (Mann Mann and Bollman Grindlay and Bollman) All this is indicative of the dependence of the liver on the portal circulation

Types and Causes of Portal Hypertension and Obstruction

Portal hypertension or obstruction to portal blood flow can be best classified by orienting it with reference to the liver The following classification makes use of this principle

I Extrahepatic
- A Prehepatic
  - Thrombosis of hepatic veins (Chiari s Syndrome)
- B Posthepatic
  - 1 Congenital
    - a cavernous transformation of portal vein
    - b congenital stricture or thrombosis of portal vein
    - c congenital hypoplasia with patent umbilical vein (Cruveilhier Baumgarten disease)
    - d hepatic portal arteriovenous fistula
  - 2 Acquired
    - a infection (phlebitis)
    - b trauma
    - c idiopathic

II Hepatic
- A Obliterative intrahepatic endophlebitis
- B Portal Cirrhosis

In the posthepatic portal vein obstruction the block may be in (1) the portal vein itself (2) its right or left branch or (3) one of its major tributaries The most important tributary that contributes to the development of extrahepatic portal bed block is the splenic vein It will be seen later that the exact site of the posthepatic portal obstruction is important therapeutically The development of collateral circulation and the hazards that these entail depend on the site of obstruction

The other classifications of clinical importance are whether the obstruction is (1) complete or (2) partial or whether it is (1) acute or (2) chronic Obviously the completeness of the obstruction depends on the site as well as the nature of the obstructing agent Thus a complete obstruction to the portal system must be situated in the main portal vein or involve both of its branches Likewise an acutely developing obstruction is more likely to be com

plete and this for two reasons (1) an acute occlusion like a thrombus is likely to occlude the entire lumen while a slowly developing process would allow recanalization (2) a slowly developing occlusion would allow for the building of local collaterals

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of numerous collateral venules The congenital form of the disease may likewise be the result of a prenatal inflammatory process The process may involve the portal vein proper or the splenic vein Regardless of the time or mode of development of the lesion there is increased pressure in the portal system distal to the cavernoma and the spleen is congested and enlarged

Congenital Stricture of Portal Vein

Congenital stenosis of the portal vein is fortunately a rare cause of portal hypertension but it is extremely serious since it affects small children and is accompanied by massive esophageal hemorrhage

Location and Pathogenesis

The stricture is usually located in the proximal portion of the portal vein at the porta hepatica This was the location of the stricture in both patients reported by Mahoney and Hogg and one of the patients reported by Rousselot One of the strictures reported by the latter was at the distal end of the portal vein but he does not elaborate on the nature of the stricture

The localization of the stricture at the proximal end of the portal vein leads to a plausible theory concerning the pathogenesis of this anomaly In the fetus the vitteline veins and the left umbilical vein and the portal vein unite at this point where the ductus venosus originates After birth the obliterative process that involves the umbilical vein and ductus venosus may extend to the portal vein resulting in a highgrade stenosis or complete obliteration

Other Anatomic Changes

The portal vein distal to stricture is markedly dilated and the strictured area may consist of a narrow fibrotic cord Mahoney and Hogg emphasize the absence of the rich collateral circulation in the porta hepatica seen in cirrhosis and cavernous changes in the portal vein The hepatic artery is increased in size and may account for the absence of atrophy of the liver The spleen is of course markedly enlarged and large varicose veins of the esophagus can be demonstrated anatomically as well as clinically

Clinical Features

The first symptom that usually brings these patients to the physician is a massive hematemesis Passage of tarry stools may occasionally precede the hematemesis These serious symptoms begin characteristically, between three and five years of age The problem is one of the differential diagnosis of the causes of gastrointestinal bleeding Even at this early age peptic ulcer has to be considered although familial telangiectasis of the gastrointestinal tract as well as other ulcerative and neoplastic lesions have to be entertained The severe anemia is of no help in the diagnosis The splenomegaly should change the direction of the diagnostic thinking but an occasional leukopenia or thrombocytopenia may raise the question of a blood dyscrasia The observation of dilated or prominent abdominal veins should make one consider portal vein obstruction with bleeding esophageal varices These should be looked for and demonstrated by barium studies of esophagus and esophagoscopy Cirrhosis may be excluded by the normal liver function tests but for absolute proof liver biopsy is required

Congenital Hypoplasia of Portal Vein

This cause of portal hypertension has been discussed under Cruveilhier Baumgarten's syndrome (page 335) The hypoplasia of the portal venous system is accompanied by congenital patency of umbilical vein and followed by esophageal varices and hemorrhage

Hepatic Portal Arteriovenous Fistula

It can be readily understood that a fistula or anastomosis between the high pressure hepatic artery and the low pressure portal vein would result in a transmission of the higher pressure to the vein with resultant portal hypertension and yet I have not seen this defect mentioned as a cause of portal hypertension This oversight is due to the rarity of this condition in man Such a case has recently been reported (Strickler et al) demonstrating that it is a real

and not a nebulous clinical entity The interest in this problem also stems from the fact that (1) this fistula has been produced experimentally (2) it may offer a new approach to our understanding of hepatic physiology and hemodynamics and (3) it has been advocated as one form of treatment of hepatic artery aneurysm

Clinical Features

The case reported by Strickler Lufkin and Rice in April 1952 is apparently unique in medical annals The patient was a female age 49 whose first complaint was abdominal distention apparently due to ascites This required numerous paracentheses which yielded clear straw colored fluid of low specific gravity and low protein content At first roentgenograms of the esophagus were negative for esophageal varices Upper gastrointestinal hemorrhage began several months after the ascites became manifested Exploratory laparotomy before hemorrhage began failed to reveal liver abnormality either grossly or histologically This was confirmed by laboratory tests

The repeated exsanguinating hemorrhages called for drastic measures but because of the patient s poor condition portocaval shunt was not performed and devascularization of the stomach was accomplished by tying many of the vessels of the upper portion of stomach The patient improved temporarily but died about one week after surgery

Pathology

The outstanding pathologic features were the gross normality of the liver with the exception of a slight increase in size and an enlargement of the left lobe which was larger than the right Microscopically the liver was normal The size of the spleen was not mentioned

The startling changes were in the vessels of the liver The branches of the portal vein were larger than the common portal vein The right branch was markedly dilated and showed a saccular dilatation at one point with calcification In this dilated calcified portion of the right portal vein there was a 2 mm opening connecting it with a dilated and tortuous hepatic artery Esophageal varices with ulcerations were demonstrated as the source of hemorrhage

Strickler and his associates postulate that the patient had a congenital aneurysm of the hepatic artery which eventually became adherent to the portal vein Following erosion into the vein portal hypertension developed leading to esophageal varices and death The pathogenesis of the ascites remained unexplained

Interest is attracted to this case not because of the unique cause of portal hypertension only but because of the possibility that trauma and acquired hepatic aneurysm may lead to a similar sequence of events This case posts a warning against the surgical formation of an arteriovenous fistula as treatment of hepatic artery aneurysm At best this procedure would delay death of the patient until portal hypertension and bleeding esophageal varices developed Portocaval shunts are contraindicated in such eventuality since by moving the arteriovenous fistula closer to the heart and getting around the damping effect of the liver rapid cardiac failure may result

Experimental Observations

Schilling and coworkers succeeded in producing an end to side anastomosis between the hepatic artery and the portal vein in dogs This significantly increased the oxygenation of the portal blood to 60 1 % as compared with 48 2 % in the vena cava and at the end of 18 months three dogs showed no significant abnormalities either in hepatic function or vascular dynamics The portal venous pressure was reported as normal but one dog showed a portal vein pressure of 20 0 cm of water which is above normal Aneurysmal dilatation of the portal vein at the site of anastomosis and general dilatation of the vein was observed and is a sign that the vein was being subjected to higher pressure

ACUTE OCCLUSION OF PORTAL VEIN

Introduction

Occlusion of the portal vein or its main tributaries with resultant posthepatic portal bed block is best divided into the acute and chronic forms The acute form is less common

of numerous collateral venules The congenital form of the disease may likewise be the result of a prenatal inflammatory process The process may involve the portal vein proper or the splenic vein Regardless of the time or mode of development of the lesion there is increased pressure in the portal system distal to the cavernoma and the spleen is congested and enlarged

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It can be readily understood that a fistula or anastomosis between the high pressure hepatic artery and the low pressure portal vein would result in a transmission of the higher pressure to the vein with resultant portal hypertension and yet I have not seen this defect mentioned as a cause of portal hypertension This oversight is due to the rarity of this condition in man Such a case has recently been reported (Strickler et al) demonstrating that it is a real

intrahepatic disease Cirrhosis is a common cause of portal vein thrombosis (Table 55) An inflammatory process outside of the vein and adjacent to it may result in inflammation of the wall and by pressure produce slowing of circulation and thrombosis Inflammatory cicatrix or granulation tissue may occlude the vein This however may produce a slow gradual and hence chronic occlusion of the vein

Neoplasms may produce occlusion of the portal vein by tumor thrombus or embolism This may be quite sudden and acute Malignant neoplasms may occlude the vein from the outside by compression Benign tumors and cysts by their gradual expansion may produce occlusion of the portal vein but this would probably be a chronic rather than an acute or sudden process

Trauma is more likely to result in chronic occlusion of the vein The only exception to this is probably surgical trauma with the necessary ligation of the portal vein Abdominal operations are a common cause of portal vein thrombosis (Table 55) A non penetrating blow to the abdomen could conceivably injure the intima of the portal vein sufficiently to result in pylethrombosis Usually however trauma would result in a slow process with cicatriza tion and gradual chronic non thrombotic occlusion

A change in the coagulability of the blood represents a classic factor causing pure pyle thrombosis Foremost among these diseases is polycythemia vera In a recent survey mesenteric thrombosis occurred in 94% of cases of polycythemia (Stroebel et al 1951) Thrombocytemia or any disease accompanied by increased numbers of platelets will stimulate intravascular clotting The phlebothrombosis seen in carcinoma of the pancreas may be due to altered clotting mechanism and involve the portal vein Pancreatitis may result in pyle thrombosis either because of the inflammatory process or because of changes in the clotting mechanism

Pathology

The pathology depends upon the primary condi tion responsible for the occlusion and on the nature of the occlusion The portal vein distal to the occlu sion may be dilated and if the occlusion has existed for some time collateral circulation is evident There may be a compensatory enlargement of the hepatic artery Unless the liver is the seat of pre-existing disease it shows no abnormality (For the morpho logic changes of hepatic infarct see p 33) The spleen is enlarged and shows evidence of congestion The thrombus may vary in nature according to its age and the etiologic factors involved If an acute in flammatory process is responsible the vessel wall will show inflammatory changes

TABLE 55
Causative Factors in Chronic Thrombosis of the Portal Vein 61 Cases

No apparent cause		13
Possible or proved causes		48
Cirrhosis	19	
Abdominal operation	14	
Malignant lesion	8	
Biliary tract disease	8	
Polycythemia vera	5	
Pylephlebitis	4	
Congestive heart failure	3	
Chronic pancreatitis		
Syphilis		
Trauma	2	
Chronic hemolytic jaundice	1	
Duodenal ulcer	1	
Ingested phenol	1	
Thyroidectomy	1	
Omphalitis in infancy	1	
Subacute bacterial endocarditis	1	
Atherosclerosis	1	
Total cases	74	

In several cases two or more possible causes for in volvement of the portal veins were present

From M P Kelly H E Robertson and H Z Giffin The Role of Chronic Thrombosis of the Portal Vein and Its Tributaries in the Syndrome of Splenic Anemia Surg Gynec & Obst 85 89 1947

Clinical Features

Symptoms and Physical Findings The clini cal picture of portal vein thrombosis depends on the nature of the pre existing disease and the rapidity with which the occlusion develops Portal thrombosis may develop preterminally in portal cirrhosis but the gravity of the patient s condition and the deteriorated func tional capacity of the liver make it difficult to ascertain what influence if any the portal vein occlusion had on the clinical state This overshadowing of the clinical picture may be

differs in its clinical picture and requires a different therapeutic approach

It is obvious from the point of view of circulatory dynamics that an acute occlusion should produce more serious alteration in physiology than a chronic occlusion It is not entirely settled whether an acute occlusion of the portal vein is compatible with life in the human being although such is the conclusion that one must draw from recent observations Death of individual patients following portal vein thrombosis cannot settle this point since in these individuals death may be due to the primary disease or to extension of the thrombus to the mesenteric veins producing mesenteric thrombosis

Animal experiments are deceptive in this respect since there appears to be a species difference in the susceptibility of various animals to occlusion of the main vessels of the liver This has been alluded to before (p 337) This species difference can be further emphasized by the following observations ligation of the portal vein (1) in the frog produces little or no disturbance (2) in the rat there is a temporary slowing of circulation which returns to normal within two or three minutes (Seneviratne 1949) (3) in the dog a state of shock develops which ends in death within 45 to 70 minutes (Elman and Cole 1934) (4) in rabbits death occurs promptly after portal vein occlusion and (5) a species of monkey (Macaca Mulatta) survive this procedure without too much difficulty (Child et al 1950)

The observations in the dog indicate that this animal goes into a state of shock accompanied by very low blood pressure from which he does not recover This apparently is due to the exclusion of the large pool of blood from the general circulation Of the 25 monkeys in which the portal vein was occluded by Child and coworkers 19 survived The six deaths are attributed either to anesthesia (sodium pentobarbital) or to other causes not related to the venous occlusion A postoperative drop of arterial systolic blood pressure of 20–30 mm Hg was observed which returned to preoperative level in one to four hours It is suggested that in this animal as well as in others that survive this procedure sufficient collateral circulation is quickly available to carry at least a portion of the excluded blood back to the heart It is also of interest that the liver remained normal The portal vein pressure in these monkeys which normally varies between 9 and 18 cm of water rose immediately postoperatively to 24–57 cm But this high pressure dropped quickly and only a slight portal hypertension (1–2 cm of normal saline) persisted In keeping with this gross enlargement of the spleen did not occur in any of the animals

Child and coworkers likewise ligated the portal vein at the porta hepatica in two patients suffering from metastatic carcinoma Neither of these two patients suffered any untoward effects attributable to the venous occlusion Liver function tests did not show marked abnormality But since these patients lived only two and a half and eight months postoperatively and suffered from malignant disease some changes did not have time to develop and some may have been obscured by the primary disease It is nevertheless obvious that no drastic immediate effects were present and the subjects survived the acute interruption of the portal vein

Because of the foregoing observations it seems likely that many of the dramatic symptoms startling findings and drastic sequelae that have been attributed to acute portal vein occlusion (thrombosis) are due to either the concomitant disease or extension of the thrombus to the mesenteric veins Nevertheless hepatic infarction can occur from occlusion of a branch of the portal vein (p 338 and Fig 63)

Etiology

Infection or inflammation of an acute and suppurative nature leads to pylephlebitis rather than pylethrombosis In the former the acute inflammatory process dominates the picture and the secondary or primary liver abscesses make this a problem of hepatic suppuration Low grade non pyogenic inflammation may result in thrombosis or low grade phlebitis hence the term adhesive pylephlebitis Such low grade or chronic inflammatory process occurs in cirrhosis and in hepatic syphilis In both of these there is of course

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gen tal str cture has been d scussed in tl e preced ng chapter (p 339) The acqu red form of portal ve n obstruct on is usually caused by fibrous obl terat on of an acute thrombos s of the portal ve n or one of its ma n tr butar es The factors that start th s process are there fore s m lar to the causat ve factors involved in the acute process namely nfect on trauma or neoplasms (Table 55) Blood dyscras as and cond t ons alter ng the coagulab l ty of the blood are more l kely to result only n the acute occlus on It s also conce vable that scars fol low ng trauma inflammat on or ben gn neo plasms may occlude the ve n gradually and slowly w thout intervention of thrombos s except n the final stage when the vessel s nearly closed W lcox and coworkers reported an unusual cause of post hepat c portal ve n obstruct on The pat ent had numerous injec t ons of sod um morrhuate to close a pancreat c fistula The portal ve n became involved n the pancreas

Pathology

The pathology of post hepat c portal bed block may be most conven ently d v ded nto (1) the pr mary d sease or cond t on produc ng the obstruc t on ( ) the s te and nature of obstruct on (3) the effect on o her organs and (4) the co ateral c rcula on

The p mary facto caus ng the occlus on such s a cyst ben gn tumor or scar t ssue from an njury nay st l be found as a tell ta e of the o g n of the ent re process Wh pple (1945) found a post trau mat c to n and c catr zed pancreas obstruct ng the splen c ve n w th a c catr x

The exact s te of obstruct on rather than the type of obstruct on s mportant s nce the s te of ob struct on p ed cates the de elopment of the collateral c rculat on and determ nes the most effect ve surg cal procedu e The obstruct on may be anywhere along the ma n po tal ve n o e ther one of ts ma n branches or along the splen c ve n Because of ts g eater length and g eater vulnerab l ty the ac qu ed post hepat c obstruct ons are mo e f e quently n the sp en c e n Th s was the obse at on of Rousselot (940) but all of L nton s 40 cases of ex rahepat c block nvo ve l the po al ve n

The spleen s the organ ch efly nvol ed n the post hepat c b ock Th s organ s n a ably en larged and may re ch cons derable s ze M cro cop c lly t s noted that the venous s nuses are w dened and engorged and along w th the ncreased strom resul n comp ess on of the splen c pu p Th s mpe les the flow of blood from the arte al system nto the pulp spaces w th consequent hemor rhages about the trabecular arteries and at the pe r phery of the fol cles The resultant nodula a eas of fibros s a ound lymph foll cles are the so-called fib o aden e of Bant

Collateral Circ lation

The collateral c rculat on wh ch has been d scussed n general terms before (p 334) w ll be approached from a sl ghtl d fferent v ew po nt here and for the sake of conservat on of space and greater clar ty the collateral c rcula t on in ntrahepat c block will also be d scussed here The d v s on of the collateral c rculat on nto two ma n groups hepatopetal and hepato fugal dates back to I ck who ntroduced t n 1909 These terms are analogous to the terms used in phys cs centripetal and centr fugal w th l ver (hepato) replac ng the centr

Thus the hepatopetal collateral ve ns are d rected toward the l er and come into play when the obstruct on s extrahepat c The blood can be shunted through the l ver v a the so called accessory ve ns of Sappey wh ch pass through the per toneal cover ng of the l ver Other ve ns that carry blood nto the l ver under these c rcumstances may be

1 the deep cyst c ve ns
2 the ep plo c ve ns
3 the hepatocol c ve ns
4 hepatorenal ve ns
5 d aphragmat c ve ns
6 ve ns of suspensory l gament

The hepatofugal collateral ve ns shunt blood away from the l ver These collateral channels are used exclus vely when the portal block s intrahepat c and are used n posthepat c block n conjunct on w th the hepatopetal c rcula t on The hepatofugal c rculat on has been d v ded into three ma n groups by McIndoe

1 Ve ns located at the s te where columnar ep thel um jo ns w th squamous ep thel n n the gastro ntest nal tract
   a card a coronary ve ns of stomach empty nto the e ophageal plexus thence into azygous and finally nto vena cava
   b anus the infer or nesenter c jo ns w th the m ddle hemorrho dal and thence into infer or vena cava

These are the most mportant pathways from the cl n cal po nt of view s nce they are the

true in other grave diseases Gradual occlusion allows for compensatory collaterals to develop and the clinical state is colored by the catas trophe of the vulnerable collateral channels

If the portal vein becomes occluded sud denly the symptoms may suggest an acute surgical abdominal emergency There is inter ference with venous drainage from the intes tines even in the absence of extension of the thrombus to the mesenteric veins and hence severe abdominal pain tympanitis and vomit ing occur Hematemesis may accompany these symptoms but is not as frequent or as serious as in the chronic occlusion and is not due to esophageal varices Diarrhea may be present and stools may contain blood especially if mesenteric vein thrombosis has supervened

Ascites has been described as a frequent finding in portal vein thrombosis Since ascites does not occur after experimental portal vein occlusion or in the chronic occlusion in man it is probably not due entirely to the venous occlusion but to other accessory factors Tympanitis which is present may be confused with ascites The liver does not enlarge unless it has been previously involved The spleen is almost always enlarged but it may be difficult to palpate in the presence of tympanitis ascites or marked abdominal tenderness Prominent superficial veins are more characteristic in the chronic form but they have been described in the acute occlusion

Other physical findings and laboratory data may point to the etiologic disease The primary disease should be sought for, because this points to the direction in which treatment is to proceed

Treatment

The treatment depends on the character of the occlusion and the nature of the etiologic disease If the occlusion is due to a thrombus and this is not neoplastic the treatment is to be directed to decreasing the coagulability of blood If polycythemia is the primary disease radioactive phosphorous should be adminis tered Heparin 50 mg is given intravenously every six hours Dicumerol 300 mg is adminis tered orally Both anticoagulants should be given simultaneously until the dicumarol (dicoumarin) becomes effective The dicumarol is reduced according to the prothrombin time

If the occlusion is due to a cyst or benign tumor their removal surgically may relieve the venous occlusion In general in the non *thrombotic occlusion the problem* is that of chronic posthepatic portal hypertension the treatment of which will be discussed later (Chapter 50)

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Acquired Chronic Occlusion of Portal Vein

Post hepatic Portal Obstruction

The chronic form of occlusion of the portal vein or one of its tributaries re sulting in chronic portal hypertension is among the most important of the lesions involving the portal vein because of its tendency to hemor rhage from dilated collateral venous channels This complication which is now amenable to surgical therapy results in diagnostic confusion with portal cirrhosis

Etiology

The congenital form of chronic portal vein occlusion cavernous transformation and con

Pathogenesis of Portal Hypertension in Cirrhosis

The pathogenesis of portal hypertension in cirrhosis has been baffling observers for many years and the problem has not been unequivocably solved as yet.

Theory of increased arteriovenous shunts. Herrick in 1907 made the startling observation that in the cirrhotic liver there is freer communication between the finer branches of the hepatic artery and portal vein than in the normal liver. This occurs through dilated capillaries and is accompanied by a relatively increased flow of blood through the hepatic artery. Thus the higher arterial pressure is transmitted to the venous channels with formation of portal hypertension. He thought that in the large cirrhotic livers there is no obstruction to portal vessels from fibrosis. Dock in part confirmed Herrick's observations inasmuch as he found the hepatic arterial bed and its perfusability increased and expressed the opinion that if the arterial inflow were reduced the portal hypertension would likewise be reduced.

That such derangement is possible is brought out by the recent observations of Knisely (1949) on the transilluminated frog's liver as well as the older observations by Wakin and Mann (194) on the amphibious and mammalian livers. The hepatic sinusoids which are lined by Kupffer cells receive blood from a portal venule and a hepatic arteriole which is wound around the venule in spiral fashion. The venule and arteriole are connected by anastomotic vessels which are contractile and can thus regulate the flow from one vessel to the other. Since the pressure is higher on the arterial side one would expect this flow to be ordinarily in the direction of the vein.

The sinusoids therefore receive a mixture of arterial and venous blood. But the amount of blood flowing through the sinusoids and the character of the mixture is regulated by the following mechanisms: (1) afferent inlet sphincter guarding the junction with the portal vein, ( ) efferent outlet sphincter at the junction with the central vein, (3) sleuce channel (Deysach's) with a common outlet to the central vein or the sublobular vein and (4) the contractility of the arterioles, venules and anastomotic vessels.

The outlet and inlet sphincters can control the total blood leaving or entering the liver and because of the vascular capacity of the liver can control the circulating blood volume by storing or discharging blood. When the hepatic arteriole contracts the sinusoidal blood is chiefly venous while with arteriole dilatation and contraction of the venule the sinusoids get chiefly arterial blood. Thus infinite variations of the vasomotor state of these vessels results in various proportions of venous and arterial blood. When the terminal arterioles are constricted while the hepatic artery is dilated and the anastomotic branches are open, arterial blood flows into portal venules and the arterial blood reaches the sinusoids through the portal system. A constantly increasing flow of arterial blood in this direction would increase portal venous pressure and fit in with Harrick's theory.

Theory of intrahepatic portal venous compression. McIndoe in 1928 performed perfusion experiments on normal and cirrhotic livers and concluded that the fibrous bands and regenerating liver nodules compressed the portal venous channels with resultant portal hypertension. Perfusion of blood through the portal vein resulted in only 13% recovery from the hepatic vein while perfusion through the hepatic artery resulted in much greater recovery. In normal livers all of the perfusion fluid is recovered. This theory is the most widely accepted one. It is easy to visualize how a portal or periportal fibrotic process can compress the radicals of the portal vein.

Theory of intrahepatic hepatic venous compression. Recent observation by Madden and associates (195) on injected cirrhotic livers yields the startling information that at least in individuals with ascites the intrahepatic portal vein bed is not only not decreased but is actually increased in volume while the tributaries of the hepatic vein are markedly decreased. The conclusion is therefore drawn that the picture of portal hypertension and ascites depends not on obliteration of the afferent venous channels but the efferent. It is difficult to conceive how a process so widespread as portal cirrhosis would obliterate one venous channel and spare another one adjacent to it. Admittedly this theory would explain the

source of critical hemorrhage and result in therapeutic problems

2 Parumbilical vein in the round ligament of the liver from the obliterated fetal circulation connects with the abdominal veins which carry the blood into the epigastric veins and the inferior vena cava

3 Veins from portions of gastrointestinal tract that become retroperitoneal developmentally or become adherent to abdominal wall thus carrying the blood through posterior or anterior parietal vessels and into the vena cava

Development of esophageal varices and the subsequent hemorrhage from them depends on the increased portal pressure which is transmitted to the coronary veins and thence to the esophageal venous plexus Portal pressure ↑ → coronary vein pressure ↑ → esophageal venous pressure ↑ → hemorrhage This sequence of events can always occur when the block is intrahepatic or at the hilum of the liver When the block is distally (post hepatic) the coronary veins may be proximal to the block and therefore not subjected to the increased pressure This is always the case when the obstruction is in the distal portion of the splenic vein and at the hilum of the spleen In this type of block esophageal hemorrhage cannot occur If the block is in the proximal portion of the splenic vein the development of hemorrhage depends on the origin of the coronary veins relative to the block The coronary vein may arise from the portal vein in 68% of instances at the junction of the portal and splenic veins in 8% and in distal portion of the splenic vein in 24% (Fig 61) It must be remembered therefore that the coronary veins must be distal to the block for esophageal varices to develop This is also true of the development of dilated hemorrhoidal veins since the inferior mesenteric vein may empty into the superior mesenteric and thence into portal vein or empty into the splenic vein The anatomical variation may result in its exclusion from the increased pressure of a splenic vein block

Clinical Features

The clinical features that are common to all forms of chronic portal hypertension are splenomegaly with the accompanying leukopenia and thrombocytopenia which is seen in some cases and the anemia which depends on hemorrhage from one of the collateral veins This comprises the symptomatology of the old Banti s syndrome The anemia may be absent if hemorrhage has not occurred yet or if the obstruction is distal so as to exclude the vulnerable collaterals (see above) Since the splenic enlargement depends on the impaired venous drainage from this organ the term congestive splenomegaly has been applied to it The leukopenia and thrombocytopenia do not occur in all cases but when they occur have been attributed to hyperactivity of the spleen hence the term hypersplenism which is contested by some

Ascites is not a usual feature of the post hepatic portal hypertension but is more likely to be seen in the intrahepatic type (portal cirrhosis) The finding of ascites should lead one to consider intrahepatic block (cirrhosis) The differentiation of this syndrome from the intrahepatic type of portal hypertension depends on the exclusion of hepatic disease by the clinical picture liver function test and liver biopsy This as will be seen later is not an easy task The clinical detection of esophageal varicosities as well as the clinical features of hemorrhage from them will be discussed below

Intrahepatic Portal Obstruction (Portal Hypertension Intrahepatic Type)

Diffuse disease of the liver is the commonest cause of portal hypertension About 30% of patients with portal cirrhosis develop hematemesis as a result of this 73% of Blakemore s (1952) 160 cases had intrahepatic portal block While portal cirrhosis is the commonest offender other forms of cirrhosis (biliary post necrotic and pigment cirrhosis) may also be responsible for this complication Rarely hepatic syphilis and prolonged hepatitis may eventuate in bleeding esophageal varices resulting from portal hypertension Sarcoidosis of the liver has been reported as a cause of the intrahepatic type of portal hypertension (Dunlap et al 1952)

for the hemorrhage. A history of alcoholism or severe malnutrition may point to cirrhosis. Likewise a history of jaundice, hepatitis, or chronic exposure to hepatotoxic agents may call attention to the likelihood of diffuse hepatic disease.

Findings pointing to hepatic involvement. Evidence indicating hepatic involvement is very valuable in establishing a specific diagnosis, for not only does it place the portal bed block in the liver, but in upper gastrointestinal hemorrhage of unknown etiology it points to bleeding from esophageal varices.

The size of the liver is of no great help since it may be large, small, or normal in size and the main pathologic process may still be in this organ. If it is definitely enlarged and especially if accompanied by splenic enlargement, it helps to confirm the opinion that intrahepatic pathology is responsible for the clinical picture.

Other clinical signs of diffuse liver disease should be looked for and, if found, will steer the physician into the proper diagnostic channel. Among these valuable signs are jaundice, spider naevi, palmar erythema, and fetor hepaticus. It should be recalled that hepatic syphilis, which may cause portal hypertension and bleeding esophageal varices, rarely shows spider naevi. Patients with portal cirrhosis who so frequently show the above mentioned sign may not show them in spite of bleeding from esophageal varices. Indeed, this catastrophic complication may be the first symptom of illness.

Liver Function Tests

Laboratory tests may show, in addition to the anemia, the other findings of hypersplenism, leukopenia and thrombocytopenia. The liver function tests may be disappointing in their failure to yield evidence of parenchymatous liver disease. From the laboratory as well as from the clinical point of view, bleeding esophageal varices may appear in a patient with minimal evidence of cirrhosis. The flocculation tests may be normal or only slightly elevated. Bromsulfalein clearance is one of the more sensitive tests in this phase of cirrhosis. We found slight elevation of the gamma globulin in such cases when all the other tests were within normal limits. This scarcity of evidence pointing to cirrhosis in some of these patients is responsible for the tenacity and usefulness of the term Banti's syndrome in reference to them. One occasionally encounters exsanguinating hemorrhage from esophageal varices due to cirrhosis without clinical or laboratory evidence of cirrhosis, and the correct diagnosis may be made only at autopsy.

Demonstration of Esophageal Varices

X ray and endoscopy are the final techniques by which the presence of varices are demonstrated. Both techniques are used in conjunction and supplement rather than supplant each other. On occasion I have seen both procedures fail to reveal varices only to have the patient exsanguinate from them later on.

The roentgenographic demonstration is less troublesome to the patient and should generally be used before endoscopy. Special media are used for their demonstration, among which are thick barium sulfate paste or rugar, a commercial preparation of thick barium. We have recently used a mixture of barium, water and carboxymethyl cellulose (Kirsh and Spellberg).* This forms a thick tenacious mixture which goes through the esophagus slowly and has a tendency to adhere. The presence of varices is revealed by a scalloping of the silhouette of the barium filled esophagus. Small oval filling defects and widening of the longitudinal folds all point to the presence of varices (Fig. 76). Reliance must not be placed solely on fluoroscopy, but films should be made as the barium passes down the esophagus. The Valsalva maneuver increases the venous pressure and helps to bring out the varicosities. The erect position has the advantage of increased pressure in the vein, but in the recumbent position the bolus of food goes down more slowly and the area can be visualized more leisurely. Esophageal varices may be very extensive, reaching from the cardia to the upper third of the esophagus.

One should not be satisfied with roentgen

* 2.5% carboxymethyl cellulose and 97.5% barium sulfate are used. 4 oz of this powder mixed in $1\frac{1}{2}$ oz of H_2O for demonstration of varices.

formation of ascites better than McIndoe's theory (p 396)

Another unsolved problem is the relative importance of hyperplastic liver tissue and fibrosis on the vascular impairment Compression from the newly formed liver nodules has been favored as the cause This fits with the development of portal hypertension in post necrotic cirrhosis where massive hyperplasia occurs but fibrosis is minimal However I have seen massive exsanguinating hemorrhage from esophageal varices in patients with a good deal of fibrosis but minimal necrosis and regeneration

Clinical Features

The clinical features of portal hypertension due to hepatic block consist essentially of all of the features of portal hypertension plus the features of diffuse liver disease and most frequently portal cirrhosis It has been repeatedly stated in the literature that extrahepatic portal bed block is diagnosed in the absence of evidence of liver disease Actually this is an oversimplification Hemorrhage from esophageal varices may be the first and at times the only symptom of cirrhosis and one may be hard put in some cases to find other evidence of liver disease

Esophageal varices Hemorrhage from esophageal varices usually becomes manifested by massive hematemesis Occasionally smaller hemorrhages may be accompanied only by melena The vomitus consists of fresh blood and undigested clots in contradistinction to *peptic ulcer hemorrhage in which the blood* is changed by contact with gastric hydrochloric acid into the coffee grounds material Of course some of the blood from the esophagus oozes down into the stomach and is then changed into the coffee grounds material While massive bleeding from esophageal varices is rare without hematemesis I have seen such a patient exsanguinate without vomiting any blood A picture of shock with low blood pressure and tachycardia accompanies the severe hemorrhage Occasionally a history of mild dysphagia may be obtained when the varices are very large

Why of all the collateral venous circulation is bleeding so troublesome *from esophageal* varices? The factors of trauma mechanical thermal and chemical play a greater role here The ingestion of rough hard poorly masticated food may result in an abrasion which leads to ulceration The ingestion of hot or chemically irritating foods like alcohol or spices may also damage the esophageal mucosa Finally the experiments of Wangensteen on rabbits suggest that the acid pepsin factor may play a role in the pathogenesis of hemorrhage from esophageal varices by its digestive effect on the mucosa

Hemorrhoids The varices developing at the other orifice although subject to trauma are rarely troublesome from a clinical point of view I have never seen severe hemorrhage from this source in a patient with cirrhosis, although I have seen one severe hemorrhage from hemorrhoids requiring blood transfusions in a non cirrhotic person

Abdominal veins Visible engorged abdominal veins can be identified in the various types of portal hypertension With infra red photography these veins are more easily demonstrated Fig 73 A network of abdominal veins may be visualized by using dark red glasses the type used for ocular accommodation for fluoroscopy when nothing obvious can be detected with the naked eye The current of blood in the abdominal veins in portal obstruction is away from the umbilicus i e upward in those above and downward in those below the umbilicus

Spleen Splenic enlargement is present in all *types of portal hypertension, and cannot* be used as a differential point in the intrahepatic type of portal bed block except that the spleen is likely to be larger in isolated obstruction of the splenic vein A point worth remembering is that after an exsanguinating hemorrhage the spleen decreases in size and therefore may not be palpable at the time of hemorrhage but becomes palpable when the blood volume is restored Therefore the spleen should be looked for frequently and one should not be satisfied with one negative finding

History pointing to hepatic disease Historical data may be of help in deciding that there is an intrahepatic portal vein block which accounts


Fig 65 A tsd aw g of a e ve ph g as seen oph g cop n a p n w h p a ho s

worth tl e r k I have not del berately gastro scoped pat ents w th esophageal v r ce but I feel sure I mu t have done th s na l ertently v thout an untowar l results In tl e absence ot roentge ograph c and endoscop c ev dence of esophageal var es gastroscopy should always be performed I l ave recently found gastr c var ces n tl e stomach by gastroscopy vl en they could not be v sual zed by the other techn ques Tl e pat ent had a splenorenal sl unt and the c rrhos a d portal h pertens on ere proven at surgery (fig 6 p 5)

Roe ge l is alt a o a l Press re D nam cs of Por al l e

Portal ve ograph X ray v ual zat on of portal ve n and ts tr butar e b nject on of rad opaque e l un s one of the recent add t ons to tl e sc ence of va ography (F g 66) The portal ve n has been filled by contrast ed a by nject on (1) tl rough saphenous e n n a pat ent th su g cal po to-ca al shunt (I ar nas 1947) ( ) tl rougl patent umb l cal ve n n a ca e of Cru e ll e Bau garten syn drome (Cel et al 1948 p 335) (3) through the coronary ve ns of sto acl (Blaken ore and Lord 1945) an l (4) th ough portacav l ana tomos s (Dotte et al 1950) More recently (1951) two papers were publ hed n the san e s e of *Ra l olo* leal ng w tl portal venography (Ch l l et al and Moore and Br denl augh)


F 66 Roe genog am of portal n a d trib aries a p m em pecim n ec ed w h 0% n of sod m od d (F om C fi n A h S g 6 449 1950)

The procedu e an l e n ar zed as follo s 35% D odra t s the op que med m employe l o or 40 cc of th s s njected througl a 15 gauge nee lle or tl o gl polythene catheter The nject on mu t be done rap dly th n t o or three seconds and x ray exposu es ade n med tel tl ereafter The catheter in serte l nt the super or n esenter c ve n and the nject on n ade w th I uer syr nge

The u eful ess of the p ocedure cannot l e full app ec ated unt l t l as been employed more extens ely It sl ould be capable of de nonstrat ng the follow ng

1 exact s te of extrahepat c portal block level of nsert on of the le ser tr b tar es nto portal or splen c ve n
3 extent and d str but on of collateral c r culat on
4 space-occupy ng ntrahepat c les ons tu mors and cysts
5 marked var at ons n s ze of lobes of l ver

By n eans f portal venography the stream l n ng of portal l lood flow has been confirmed In o e ca e of c rrho of the l er it as note l that the finer enous channel d d not fill too well th s ma becon e a s gn ficant ob ser at on f fo n l fre juentl n portal c rrho s The ra l paque mater al w th n the l er del neate its ze



Fig 64 Roentgenogram of barium filled stomach showing varices in fundus in a pati nt with portal cirrho i and bleeding esophageal varice (F om Spellberg Rev Ga troenterol 19 77c 1951)

inspection of the esophagus only for varices may occur in the stomach as well It is important to determine the presence of gastric varices for this may modify the therapeutic approach In this organ the varices are usually in the fundus and reveal themselves as a cluster or rosette of radiolucent filling defects (Fig 64) They are also best brought out by the Valsalva maneuver and this technique can help to distinguish them from polyps which would not change in size by increasing the intra abdominal pressure Large varices may present themselves roentgenographically as filling defects in the fundus of the stomach resembling neoplasm even in the absence of demonstrable esophageal varices (Cohn 1951)

Esophagoscopy like roentgenography demonstrates not only the presence of varices but their distribution number and size (Fig 65) This procedure is slightly more accurate than X ray in revealing the presence of varices Although it is a more trying procedure for the patient it has the further advantage that therapy may be carried out through it

Gastroscopy has been recommended by some in all cases of suspected or demonstrated esophageal varices to determine the presence of gastric varices Esophageal varices have been regarded as a contraindication to gastroscopy because of the danger of trauma with resultant hemorrhage but Moersch thinks that the risk is not great and the advantage gained is

of liver disease (p 85) Since cirrhosis which is the commonest cause of intrahepatic block may be in a latent state needle liver biopsy may be necessary for a diagnosis If the evidence points to hepatic involvement one must differentiate the type of lesion responsible for the hepatic portal bed block among these are (1) portal cirrhosis (2) biliary cirrhosis (3) post necrotic cirrhosis (4) hemochromatosis (5) hepatic syphilis (6) sarcoidosis and (7) schistosomiasis The diagnostic features of these are discussed in the corresponding sections While the determination of the specific agent responsible for esophageal varices is of interest it is more of theoretical than of practical importance for the treatment in most instances is essentially the same

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  7 Esophageal ulcerations and neoplasms
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  1 Purpuras
  - Hemophilia
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  4 Leukemias
C Deficiency diseases
  1 Scurvy
  Hypoprothrombinemia
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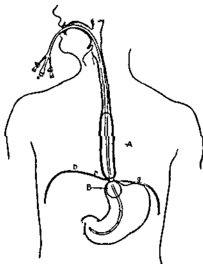


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The method of performing the test consists of inserting a needle into one of the tributaries of the portal vein one of the veins of the gastrocolic omentum or one of the mesenteric veins The calibre of the needle should be 18 gauge or at least 20 gauge if smaller it will interfere with the free transmission of pressures The structures in which the vein is embedded should not be pulled up and put under tension for this will block the venous circulation The needle is attached by a two way stopcock to a manometer and Luer syringe filled with saline The stopcock is opened and some of the saline is allowed to flow into the vein When the pressure on the Luer syringe is discontinued the direction of stopcock changed the pressure in the vein and manometer become equalized and the height of the column of saline in the monometer indicates the venous pressure

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Abnormal venous pressures have been recorded between 250 and 550 mm of water but pressures over 600 mm have been obtained If Taylor and Egbert's readings are accepted there is considerable over lapping between the lower limits of hypertensive pressure and the upper limits of the normal pressure For this reason and also because of the much greater hemorrhoidal vein pressure without hemorrhage they suggest that another factor besides increased pressure must be operating and this factor may be a congenital structural defect in the esophageal plexus

The estimation of the portal venous pressure preoperatively would be a valuable contribution to the clinical analysis of the patient Such an attempt was made by Davidson and associates They found that measurement of the pressure in one of the abdominal collateral veins with manual obstruction proximally yielded results equivalent to direct portal pressure Studies of venous pressures on the intact dog suggests a means of estimating the portal venous pressure preoperatively in man Friedman and Weiner measured simultaneously pressures in the sinusoids hepatic and portal veins of the dog The sinusoidal pressure was found to be midway between the pressures in an occluded portal and hepatic vein branch The pressure in an occluded branch of the hepatic vein was found to be several centimeters of water above that in a portal vein branch Hence hepatic vein pressure obtained by hepatic venous catheterization in man could serve as a basis for calculating the portal vein pressure

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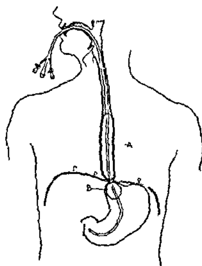


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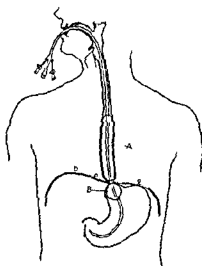


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50 — *Treatment of Esophageal Varices and Portal Hypertension*

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The treatment of esophageal varices may be divided into the following phases

1. Treatment of varices before hemorrhage has occurred
2. Emergency treatment of bleeding esophageal varices
3. Treatment directed toward varices after hemorrhage has stopped
4. Treatment of the portal hypertension

Treatment of Varices before First Hemorrhage

Vigorous treatment of portal cirrhosis in the early stages and meticulous treatment of hepatitis and other hepatic disease that may lead to the development of hepatic portal bed block may forestall the development of portal hypertension and esophageal varices If these are discovered on roentgenographic examination of a patient with cirrhosis before bleeding has occurred radical therapy directed toward the varices is not indicated immediately The treatment should be three fold and consist of (1) *vigorous treatment of the underlying disease* (2) prevention of trauma to the varices and (3) education of the patient

The treatment of cirrhosis is discussed in Chapter 77 The prevention of trauma of all kinds should be promoted by interdicting the ingestion of very hot spicy or coarse foods Proper mastication should be insisted upon Since gastric acidity may be a factor a modified ulcer regimen with frequent feedings alkalies and avoidance of alcohol should be insisted upon Various occupations in which excessive physical strain or excessive use of the respiratory apparatus such as playing a wind instrument *may tend to increase the intra abdominal* and portal pressure which may in turn increase the likelihood of hemorrhage

The patient should be educated in regard to his illness so that he is cognisant of its dangers He should not venture far from competent medical care He should know his specific diagnosis so that if a hemorrhage develops in the absence of his physician he can inform his new physician about the probable source of the hemorrhage

Emergency Treatment of Hemorrhage

The emergency treatment of esophageal varices hemorrhages consists of factors utilized in all types of hemorrhage some are modified and others are unique This phase of treatment may be subdivided into the following

a absolute bed rest
b Trendelenburg position has been advised to decrease the pressure in the esophageal plexus

My personal experience with this is limited and unfavorable but since it is easy to employ it should be included in the treatment

c feeding should consist of cool liquids or nothing by mouth if hemorrhage is brisk and more active procedures become necessary
d mild sedatives should be administered but *not barbiturates* (p 577)
e blood transfusions should be administered slowly and cautiously if blood loss is considerable It is better to allow the patient to suffer a mild anemia of around

quickly detected by the history of deficiency gum changes painful joints marked increase of capillary fragility and low blood and urinary ascorbic acid levels *Bleeding from hypo*prothrombinemia and increased capillary fragility may occur in liver disease and therefore in its presence these subtler causes of hemorrhage should be considered Every patient with hemorrhage should have a pro*thrombin time determination*

A carefully elicited history should enable one to determine that the respiratory tract is the source of bleeding Observation of the patient would indicate that hemoptysis is present Examination of the nose should detect a bleeding ulcer in this region A history of poisoning should be easily obtainable from the patient or *family the state of pharyngeal mucous mem*brane may indicate that a corrosive agent was ingested Systemic infections should not be much of a problem since fever and the acute onset of a debilitating illness precede the hemorrhage In yellow fever and Weil s disease the liver may be the responsible factor in the hemorrhagic phenomenon But in these diseases the bleeding is due to chemical changes rather than anatomical changes in the esophageal veins

The differentiation of bleeding from gastric lesions and especially peptic ulcer is much more difficult This is by far the commonest cause of upper gastrointestinal hemorrhage about 90% of which is due to this lesion The age of the patient may be of help since many *ulcer patients bleed in the third decade* while cirrhosis is uncommon until after the age of 40 Post necrotic cirrhosis is the exception A *history of typical ulcer dyspepsia or previous roentgen diagnosis of peptic ulcer is helpful* A period of epigastric distress prior to hemorrhage which subsides after the hematemesis speaks for peptic ulcer A history of alcoholism hepatosplenomegaly spider nevi jaundice fetor hepaticus leukopenia thrombocytopenia favors esophageal varices However even in the presence of far advanced hepatic disease upper gastrointestinal hemorrhage may be due *to a concomitant ulcer* (p 511)

At present I am using two other procedures for making a diagnosis If the clinical picture suggests cirrhosis with bleeding varices I insert the Sengstaken double balloon tube (Fig 67) and inflate both balloons in an attempt to compress the bleeding varices If the hemorrhage is from this source the inflated *esophageal balloon stops the bleeding* and the aspirated material from the gastric tube shows less blood and finally becomes clear *If bleeding continues unabated there are two* possibilities (1) that the bleeding is from a peptic ulcer or other intragastric neoplasm or (2) that the esophageal varices are accompanied by gastric varices

If the bleeding does not cease from the above procedure the patient should have an upper gastrointestinal roentgenogram in the re*cumbent position and an attempt* be made to visualize esophageal and gastric varice and a gastric or a duodenal ulcer or a gastric neoplasm If the roentgenographic examination *is* not diagnostic the theory of probability favors bleeding from an ulcer The safety of early x ray studies in upper gastrointestinal hemorrhage has been confirmed recently by Zamcheck and his coworkers

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The treatment of cirrhosis is discussed in Chapter 77. The prevention of trauma of all kind should be promoted by interdicting the ingestion of very hot, spicy or coarse food. Proper mastication should be insisted upon. Since gastric acidity may be a factor, a modified ulcer regimen with frequent feeding, alkalies and avoidance of alcohol should be insisted upon. Various occupations in which excessive physical strain or excessive use of the respiratory apparatus, such as playing a wind instrument, may tend to increase the intra-abdominal and portal pressure which may in turn increase the likelihood of hemorrhage.

The patient should be educated in regard to his illness so that he is cognizant of its dangers. He should not venture far from competent medical care. He should know his specific diagnosis so that if a hemorrhage develops in the absence of his physician, he can inform his new physician about the probable source of the hemorrhage.

Emergency Treatment of Hemorrhage

The emergency treatment of esophageal varices hemorrhages consists of factors utilized in all types of hemorrhage; some are modified and others are unique. This phase of treatment may be subdivided into the following:

a. absolute bed rest.

b. Trendelenburg position has been advised *to decrease the pressure in the esophageal plexus*.

My personal experience with this is limited and unfavorable, but since it is easy to employ, it should be included in the treatment.

c. feeding should consist of cool liquids, or nothing by mouth if hemorrhage is brisk and more active procedures become necessary.

d. mild sedatives should be administered, but *not barbiturates* (p. 577).

e. blood transfusions should be administered slowly and cautiously if blood loss is considerable. It is better to allow the patient to suffer a mild anemia of around

3 0 to 3 5 mil erythrocytes per cu mm than over distend the vessels and start another hemorrhage

This cautious attitude must be maintained in spite of the known sensitivity of the liver to anoxia and the danger of developing ascites from lowered plasma proteins One must cautiously walk the plank between two narrow precipices

f compression of esophageal varices by means of a balloon

Technique of Balloon Tamponade

The emergency treatment of bleeding esophageal varices by balloon compression was suggested by Rowntree and coworkers Later a triple lumen double balloon tube was proposed by Sengstaken (Fig 67) The tube is inserted through the nose into the stomach to the 55 cm mark The gastric balloon is inflated with 150 cc of air and the entire tube drawn back until it is stopped by the cardiac sphincter The tube is fixed at this point and the esophageal balloon is inflated to a pressure of 20–30 cm of mercury This pressure is sufficient to compress the esophageal veins and stop the hemorrhages Suction can be maintained on the gastric tip of the tube When bloody material is no longer aspirated it is proof that the bleeding has been controlled If the bleeding does not stop in spite of maintenance of sufficient pressure in the esophageal balloon with the balloon in the proper location it suggests that there is also erosion and hemorrhage from dilated veins in the fundus of the stomach It may be possible to compress these by further inflation of the gastric balloon (200 cc of air or more) and pulling it tightly against the diaphragm This procedure has not been successful in my hands in arresting hemorrhage from gastric varicosities When the bleeding veins are effectively compressed the tube should be left in situ with continuous inflation of the esophageal balloon for at least 48 hours The balloon is then gradually deflated if the bleeding does not recur the entire apparatus can be removed While the tube is in situ the patient can receive liquid feedings injected through the gastric tube This is a valuable supplement to the t avenous fluids (For formula see p 574)

The use of topical thrombin along with balloon tamponade has been recommended (Kenamore and Elliott Barnett and Cohen) A 1 10 solution of the topical thrombin is applied to the esophageal balloon before insertion and about 5 cc of this solution is given to patient by mouth I have utilized this procedure several times but saw no evidence that this addition was superior to the tamponade without thrombin

ELECTIVE THERAPY OF ESOPHAGEAL VARICES AFTER HEMORRHAGE STOPS

After the emergency has been weathered successfully and this phase of the treatment has met with greater success since the introduction of balloon tamponade one is ready for other procedures designed to combat the recurrence of hemorrhage These procedures are of three general types (a) procedures directed toward the veins (b) procedures directed toward improvement of collateral circulation and (c) procedures aimed at reduction of portal hypertension

(a) Procedures directed toward obliteration of esophageal veins may be subdivided into the following approaches

(1) injection of sclerotic agents
(2) ligation of submucosal veins
(3) resection of vein bearing area
(4) ligation of coronary veins of stomach

Injection of sclerosing agents into varicosities through an esophagoscope was introduced in this country by Moersch in 1940 The most commonly used substance is 5% aqueous solution of sodium morrhuate This has been done not only as an elective procedure but also as an emergency procedure during hemorrhage without untoward results and with arrest of hemorrhage (Welt 1944 Patterson 1946) Most of the reported cases had either brief follow up or had recurrent hemorrhages My personal experience with this procedure is not a happy one A period of freedom from hemorrhage may follow only to be interrupted by disappointing hemorrhage One of my patients developed a massive hemorrhage one day after the completion of a second course of injections

Crile performed trans esophageal ligation of submucosal veins after surgical exposure of the esophagus All these seven patients were young and apparently had an extrahepatic portal vein block Linton accomplished transesophageal and tran gastric ligation of varices which he approached through a left thoracotomy Gray and White ell proposed a combined surgical approach which attempts to combat several of the factors thought to precipitate hemorrhage from these varices The procedures recommended by them include (1) splenectomy (2) deva cularization of the lower part of the esophagus and cardia (3) bilateral vagotomy and (4) gastroenterostomy Phemister and Humphreys reported the resection of vein bearing area in two cases of bleeding esophageal varices where other methods of therapy failed One of the e two patients had recurrent hemorrhage while the other was followed for only three months postoperatively This procedure consi ts of resection of distal esophagus and fundus of s omach (esophageal plexus and coronary veins) It is a very extensive procedure with a good deal of surgical risk and should be reserved only for tho e cases where other procedures especially shunt operations have failed Ligation of coronary vein of stoma h will remove the chief ource of blood to the dilated esophageal plexus and thereby temporarily reduce their pressure This is a palliative procedure for eventually these channels are re established in the pre ence of the continued high portal pressure

Procedures directed toward change or *improvement of collateral circulation* include the oldest surgical procedures in this field and date back to Talma (1898) and Drummond and Morrison (189f) who introduced omentopexy a procedure that still carries their names (Talma Morrison) This operation is chiefly of historical interest newer and more effective methods have replaced it Cates reported a series of patients in 1943 with a mortality of 42% within two weeks after omentopexy In addition to its high mortality the results in those who survive are not satisfactory

The urgical production of a posterior mediastinitis to divert the blood from the sub mucosal veins to the posterior me liastinal veins has been proposed by Som and Garlock (1947) It apparently relieved the recurrent hemorrhage in their two cases This seems to be a procedure too dra tic and hazardous for wide spread use

TREATMENT OF PORTAL HYPERTENSION

Procedures aimed at reduction of portal hypertension by direct attack on the portal vein or its tributaries are more sound and are the procedures of choice in the definitive therapy as portal hypertension These include

(a) Splenectomy
(b) Ligation of splenic artery
(c) Ligation of hepatic artery
(d) Portal shunts
  (1) splenorenal anastomosis
  (2) portacaval anastomo is

(a) Splenectomy results in a 40% reduction of blood entering the portal vein and therefore should reduce the portal vein pressure temporarily Moreover the enlarged spleen may produce thrombocytopenia and leucopenia both of these are overcome by the splenectomy Splenectomy is the treatment of choice for splenic vein block close to the spleen since it removes the end organ involved with its circulatory pathways leaving the rest of the portal system intact

(b) Ligation of the splenic artery as a treatment for portal hypertension was introduced by R B Watson in 1935 It was later performed by Everson and Cole (1948) It has been recommended for patients who are poor surgical risks for the more extensive and time consuming shunt procedures Both splenectomy and splenic artery ligation preclude a splenorenal shunt later and therefore should be avoided in proximal portal vein obstruction

(c) Recently combined ligation of splenic and hepatic arteries has been recommended as an approach to the treatment of portal hypertension (Rienhoff and Berman et al 1951) These operative procedures are unique inasmuch as they are radical and courageous approaches to a eriou and baffling problem They demonstrate that man can survive ligation of the hepatic artery for some time without any obvious deleterious effects

The rationale of the hepatic artery ligation

depends on the observations of Herrick and Dock that portal hypertension is at least in part dependent upon increased arteriovenous anastomosis, and the transmission of the superior arterial pressure to the portal vein. It has also been suggested that the liver is more dependent on venous than arterial blood and the arterial ligation may improve venous blood flow. The patients are prepared by injections of antibiotics, penicillin and streptomycin, in line with the views expressed by Markowitz in his experiments on the dog. The ligation was done at the origin of the hepatic artery from the coeliac artery, before the origin of any of its branches.

The six patients reported by Rienhoff have gotten along well. One of these patients survived for three and a half years without apparent increased damage to the liver. Not only was a decreased tendency to esophageal hemorrhage observed in these patients, but a decreased accumulation of ascites was also noted. Rienhoff cites the survival of six other patients following this operation. Berman and associates added five successful ligations and divisions of the hepatic and splenic arteries. They have shown a fall of 50 to 70 mm. of water pressure in the portal system following arterial ligations. Madden and his group ligated the hepatic artery in several patients who died within six *months from other causes without evidence of* improved hepatic circulatory dynamics.

That hepatic artery ligation is not an innocous procedure in man is proven, if proof were needed, by the death of one patient following this procedure from fatal hepatic necrosis (Rosenbaum and Egbert, 195-). Jahnke and coworkers (1953) reported one patient in whom the portal venous pressure dropped immediately following ligation and division of these arteries, but the pressure in the esophageal plexus gradually rose to preoperative levels within four months.

(d) Portacaval shunts. The surgical procedures in which a shunt is created between the portal and caval systems are the most widely accepted and most widely used procedures for relief of portal hypertension and bleeding esophageal varices. The two procedures utilized to carry out this objective are (1) splenorenal anastomosis and (2) portacaval anastomosis.

Splenorenal anastomosis consists of a splenectomy followed immediately by an end to side anastomosis of the splenic vein and left renal vein with preservation of the kidney. This is the procedure of choice in extrahepatic portal vein block where the portal vein may be involved in a cavernous transformation or another pathological process which makes it unsuitable for shunt procedures. For this reason it is inadvisable to do a splenectomy alone since it makes the splenic vein unavailable for purposes of anastomosis if this should become necessary later. Recurrent bleeding after simple splenectomy is all too common with the single exception mentioned (page 357).

In intrahepatic portal obstruction there is a difference of opinion whether a splenorenal or a portacaval shunt is the procedure of choice. Some have favored the splenorenal shunt (Rousselot) as the primary operation even in intrahepatic portal obstruction since in the event of continued bleeding the portacaval anastomosis can be done at a later date.

Portacaval anastomosis is the side-to-side anastomosis of the portal vein and inferior vena cava favored by some as the treatment of choice in intrahepatic portal block (Blakemore, Linton). This procedure is technically simpler and *the anastomosis can be larger and* therefore less likely to close. The side to side anastomosis allows some flow of blood into the liver and does not deprive the liver completely of the portal blood flow. This procedure has some technical drawbacks. It is occasionally difficult to bring the portal vein and vena cava together without undue tension. This obstacle has been surmounted by the use of a vitallium tube or vein graft to bridge the gap. Preserved arterial grafts have also been proposed *for this purpose* (Southwick). This procedure can also be carried out after failure of prior splenectomy. Lesser veins have also been utilized for this purpose such as the superior mesenteric to inferior vena cava (Bogoras) or superior mesenteric to ovarian vein (Villar and Tavernier) and spermatic to splenic vein (Muersing). The handling of these small veins makes this a technically difficult procedure. Anastomosis

between a dilated right gastroepiploic vein and left renal vein was performed successfully (De Britto et al 1952)

Appraisal of Results of Newer Approaches to Treatment of Portal Hypertension

The two questions to be answered are (1) Do these procedures have a deleterious affect on the liver? and (2) Will they accomplish their purpose of keeping the portal pressure at a lower level and prevent hemorrhage from esophageal varices?

It would be surprising indeed if such radical interference with hepatic circulation as was described above should produce no deleterious effects on the liver For this reason if for no other the ideal aim should be the prevention of the e dire consequences of cirrhosis or their treatment by physiological and pharmacological means All the surgical procedures except simple splenectomy and ligation of varice must of necessity reduce the amount of blood delivered to the liver an organ already embarrassed by a relentless pathologic process which in itself interfere with its circulation Further liver damage may be expected from these meddlesome procedures Ligation of the hepatic artery at its origin apparently leaves adequate collateral circulation to prevent serious hepatic infarction But fatal necrosis from this opera on has already been reported and a return of portal hypertension has been noted It does not promise to become a practical form of therapy for portal hypertension although the limited experience with this procedure does not allow for final conclusions

Portacaval shunts have been carried out in sufficient numbers and therefore some conclusion may be justifiably drawn Moreover since the procedure actually amounts to an Eck fistula there is a larger experimental background to draw from Animals on whom the portal blood was diverted to the vena cava show

1 deficient regeneration (Mann Grindlay and Bollman)
2 deficient plasma protein and hemoglobin synthesis (Whipple et al)
3 decreased utilization of amino acids (Harper et al)
4 deficient bile salt synthesis (Smith and Whipple) and
5 decreased bromsulphalein clearance

Preshaw and coworkers showed that not only is bromsulfalein clearance in dogs impaired by shunt procedures but if all the portal blood is diverted from the liver the ability of these animals to withstand carbon tetrachloride poisoning is greatly decreased In keeping with these observations the shunt procedure in man are constructed so as not to shunt the entire portal blood supply away from the liver

After portacaval shunts in man the estimated hepatic blood flow (FHFB) decreases consistently (Bradley) The likelihood of further hepatic damage in man after these surgical procedures is emphasized by the fact that some of these patients die postoperatively from hepatic failure some immediately and some after a latent period of several months Linton s post-operative mortality figures confirm the importance of the normality of the liver In extrahepatic portal vein block where the liver is normal there was a mortality of 3 8% but in patients with intrahepatic block the mortality was 25 6% and three of these ten patients died of liver failure In Blakemore s 166 patients those with extrahepatic block had a mortality of 6 3% while those with intrahepatic block had a mortality of 1 9%

Splenorenal shunt results in venous hypertension in the left kidney which in turn shows disturbance in function The affected kidney shows decreased glomerular filtration and increased tubular salt and water reabsorption (Sirota and Nabatoff 1952)

Therefore in the selection of patient for this operation only those with adequate hepatic function should be accepted Specifically the serum albumin should be above 3 0 gm % the bromsulfalein retention should be less than 10% the flocculation tests should be normal or only slightly abnormal and jaundice should be absent or minimal Intractable ascites indicates poor hepatic function and therefore is a relative contraindication to shunt operations The other causes of postoperative death are hemorrhage and sepsis Table 56 from Blakemore shows the relationship of various liver function test to postoperative mortality

TABLE 56

Correlation of Liver Function Tests with Postoperative Deaths and Follow-up Deaths

	No. of patients	No. of postoperative deaths	No. of survivors	No. of follow-up deaths	No. followed	Mortality: Postoperative per cent	Mortality: Follow-up per cent
Serum albumin less than 3 gm %	16	6	10	3	7	37 5	33 [illegible]
More than 3 gm %	135	4	111	14	97	17 7	1 6
Ascites F	[illegible]	15	17	7	10	46 8	41 1
R	10		8	0	8	[illegible]0	0
None	117	13	104	11	93	11 1	10 5
Prothrombin time more than 4 sec above normal	51	13	38	6	3	25 5	15 8
Less than 4 sec above normal	83	15	68	7	61	18	10 [illegible]
Cephalin flocculation 3 plus–4 plus	44	1[illegible]	31	7	4	9 5	2 5
1 plus 2 plus	104	17	87	10	77	16 3	11 4
Bromsulphalein (30 min after inj) above 10%	101	4	77	11	66	3 7	14 4
Below 10%	7	3	34	3	31	8 1	8 8
Bilirubin above 1 mgm %	46	10	6	6	30	1 7	16 6
Below 1 mgm %	91	17	74	10	64	18 6	1[illegible] 6

F indicates cases that failed to respond to medical treatment Blakemore Surg Gyn and Obs 94 443 195
R indicates cases that responded to medical treatment

The preoperative preparation and post operative care of these patients should therefore be along the lines which would tend to counteract the above causes of death (1) guarding against hepatic failure by appropriate preoperative diet and postoperative fluid and vitamin administration (page 573) (2) maintenance of prothrombin at normal level by vitamin K administration and rejection of patients whose prothrombin cannot be elevated and (3) antibiotic therapy with penicillin and another antibiotics such as aureomycin or streptomycin to protect the liver as well as the other organs against the ravages of infection

Permanence of Results

The permanence of results from combined splenic and hepatic artery ligation may be questioned in view of the experience of Jahnke and associates All the other efforts at controlling esophageal hemorrhage such as splenectomy sclerosing of veins etc except for portacaval shunts are makeshift procedures without permanent effect The shunt procedures are today the most rational and most encouraging of all the surgical approaches to the problem The permanence of the shunts are not assured in all cases Splenorenal anastomoses because of their smaller calibre are more likely to close Blakemore (195[illegible]) fixed a polyvinyl catheter into the inferior mesenteric vein near the splenorenal shunt The catheter was brought out through the skin incision and used for regional heparinization This refinement of technique should reduce the likelihood of thrombosis at the shunt Portacaval anastomoses in normal dogs close in three to six weeks in one third of the animals operated upon The increased portal pressure in patients would tend to keep the anastomosis open I have seen several patients who required one procedure after another to control hemorrhage and one patient in particular who had portacaval anastomosis following a splenorenal shunt and finally gastroesophagectomy had to be done to forestall further hemorrhage

The ultimate like the immediate prognosis is worse in patients with intrahepatic portal block than in extrahepatic block There is evidence from venous pressure measurements that the portal pressure falls in some cases as much as 300 mm of water and the esophageal varices disappear roentgenographically Nevertheless

patients in both groups die from recurrent hemorrhage. Death from liver failure is an additional cause of death in those with hepatic portal bed block. Whether the shunt procedures hasten death from liver failure by decreasing the amount of portal venous flow cannot be ascertained from the available data. Only two of Linton's 50 patients died from liver failure at 8 and 19 months postoperatively while 8 of Blakemore's 55 patients died from this cause within two to four years postoperatively. 17.7% of patients died during the followup period; however, one of Blakemore's patients was alive seven years after a shunt procedure. The conclusion seems justified that the porta-caval shunts mark a definite advance in the treatment of, and prevention of death from hemorrhage from esophageal varices.

IX CIRRHOSIS

51—Definition and Classification of Cirrhosis

THE generic term cirrhosis of the liver is honored by age and usage It is however a poor term inasmuch as it may introduce confusion and misinterpretation and semantically it does not say what it means To the clinician it means a chronic progressive liver disease accompanied by diffuse fibrosis and hardening of the organ Yet cirrhosis means neither fibrosis nor hardening Indeed lay dictionaries define cirrhosis as induration or hardening of an organ The word is derived from the Greek kirrhos meaning orange or yellow brown referring to one of the less important changes in the color of the diseased organ The confusion arises from the fact that cirrhosis is confounded with scirrhous the latter is derived from the Greek skiros meaning hard It is regrettable that the largest and most important group of liver afflictions should be thus misnamed A term such as scirrhosis would more accurately describe the anatomical and clinical features of the disease The term chronic hepatitis has been proposed to replace cirrhosis and at one time I thought such a change had much to recommend it Hepatitis refers to an inflammatory process while cirrhosis is chiefly a degenerative process throughout its course and especially in the advanced phase Moreover chronic hepatitis has been correctly applied to the chronic phase of acute viral hepatitis However the time honored term cirrhosis is so firmly entrenched in the literature that it would be impossible and probably inadvisable to displace it

DEFINITION

Because cirrhosis is such a general term it is difficult to define it accurately without giving offense to either those who would restrict or those who would expand its usage Clinically it is a disease of the liver which is chronic of multiple or unknown etiology usually progressive and evidenced by varying degrees of functional impairment Portal hypertension may express itself in the form of splenomegaly superficial abdominal collateral circulation and esophageal varices the erosion of and hemorrhage from these form one of its catastrophic sequelae Ascites is a frequent accompaniment of the advanced disease and hepatic failure and hepatic coma may mark its terminal phase Pathologically it is characterized by diffuse as opposed to focal involvement of the liver fibrosis degeneration and regeneration Increase of fibrous tissue is a necessary requisite for the diagnosis of cirrhosis but not all diffuse fibroses of the liver are accepted by pathologists as cirrhosis Some claim that the fibrosis must distort the normal architecture of the liver lobule so that the relationship of the central vein to the lobule is lost The regeneration should be nodular not lobular that is it should not proceed along the normal reticulum network and not form structurally and functionally normal lobules The corollary to this

is that destruction of the reticulum framework must precede regeneration otherwise regeneration is orderly and will not constitute cirrhosis

Elias and Popper point out that several types of cirrhosis show the following anatomical alterations (1) subdivision of lobules into primary nodules by fibrous tissue septa with the central vein becoming an internodular structure (2) further subdivision of the primary nodules into secondary nodules by the cutting effect of fibrous tissue septa and (3) regeneration and multiplication of some groups of cells because of favorable blood supply and necrosis of other cells due to strangulation of the blood supply

All these limitations imposed on the definition of cirrhosis are qualitative as well as quantitative Complete distortion of the lobular architecture of the liver is seen in advanced Laennec's cirrhosis but early in the disease the lobular pattern is not completely lost If all regeneration in cirrhosis were not in functioning lobular units it would seem virtually impossible to expect improvement in function after therapy But improvement in function does take place sometimes to a remarkable degree and this would suggest that regeneration along established anatomical pathways does occur even in portal cirrhosis

In postnecrotic cirrhosis the fibrosis and collapsed reticulum may encompass a group of lobules which in themselves have a normal architectural relationship to the central vein In the so called monolobular cirrhosis the fibrosis takes place around individual lobules again leaving the architecture of the lobule intact therefore if complete alteration of lobular architecture were accepted as a requisite for a diagnosis of cirrhosis many forms of cirrhosis would have to be excluded For this reason I think the exclusion of cardiac or congestive cirrhosis from this group and insistence on the use of the term cardiac fibrosis is unjustified Moreover as is pointed out in Chapter 66 the architectural alteration in this condition may become sufficiently marked to justify the term cirrhosis even for a purist

It is true that the diagnosis of cirrhosis depends on a demonstration of certain anatomical changes but so do many other diseases yet we have to be satisfied frequently with clinical criteria The increased use of needle biopsy has expanded and will continue to extend our knowledge of liver disease though we cannot expect to identify all the precise anatomical alterations in a small specimen of liver A diagnosis of cirrhosis is justified on the basis of the clinical findings of chronic liver disease with persistent functional impairment especially when spider hemangioma and splenomegaly are present along with demonstration of fibrosis and some distortion of hepatic architecture on needle biopsy

Classification of Cirrhosis

The classification of cirrhosis is varied and because of the multiplicity is confusing The classification may be based on etiological clinical or anatomical factors There are synonymous terms for the same disease entity depending upon the taxonomic approach or independent of any rational classification

Cirrhoses and Their Synonyms

- Portal Cirrhosis
  - Periportal cirrhosis
  - Atrophic cirrhosis
  - Laennec's cirrhosis
  - Alcoholic cirrhosis
  - Nutritional cirrhosis
  - Fatty cirrhosis
- Biliary Cirrhosis
  - Hanot's cirrhosis
  - Hypertrophic cirrhosis
    - Cholangitic cirrhosis
    - Cholangiolitic cirrhosis
    - Xanthomatous cirrhosis
    - Juvenile cirrhosis
- Cardiac Cirrhosis
  - Congestive cirrhosis (Section XI)
- Postnecrotic Cirrhosis
  - Toxic cirrhosis
- Pigmentary Cirrhosis
  - Hemochromatosis (Section XII)
  - Bronze diabetes
- Monolobular Cirrhosis
- Pseudolobular Cirrhosis
- Multilobular Cirrhosis
- Zoo Parasitic Cirrhosis

not clear cut and sugge t two types of c r rhos ex t ng n the a e l er Indeed such an occu rence s w th n the realm of po s b l ty It s not ent ely unl kel fo a pat ent w th nutr onal c rrho t de elop an ob truct on of the common duct or a v r l hepat t s h ch would lea e ts gnatu e on the d to ted l er ar h tectu e The dec n a to whether b zarre hange are d e to an at p cal eact on to one facto o mult p e f cto n a b ext en el d ff ul an l at best a rema n onl a h e d conje e

The most s t fact r non enclatu e and the mo t at fact d agno cla ficat on to the cl n c an l o ld ncl de e e al a pect of the d ea e p oces un le c n de at n l th e a d the l ep tolog t wo ld do well o ad pt th e a l olog appro ch n l n l de the f ll w ng po n n l l agno of ch a well a cute l e d ea e (tom c (et o g c an l (3 funct nal For example th l e e n pat e A w th c h m be

cla s fied a (1) anatom c (portal c rrho) ( ) et olog c (nutrit onal) (3) f n t onal (l ght mpa ment)

The fun t onal n p ment can be l ded nto th ee major gro ps

C o p I Rep e ent m nor al e at n of l er fun t on te t v tho t ul ject e np ton

Cro p II Would rep esent node ate altera t n l l er funct on and me cl n cal n p t n of m nor na re h a m l l an rex a fl gab l and d pept c pto

C o p III Wo ld repre ent ma ke l alte a t o of l e test h pcalbun nen a (s g n or belo ele at on of erum l l rub n al o e and cl n cal e dence of a c te Th o ld correspond the so-call d de co pen ated c rrho

F llo v ng th cla h t on pat ent l ma al l a e po tal c rho (a t c to c et ol g) due t c l tetr chlo de th n a ke l np r ent g oup III (funct onal

F a J n cirrh S n b p of l X h w ma ked fib o and b d l p a n n a h ld n ar age pr bab a b c rrhos Co es o D P Dep rtm l a h n Un rs o I no Sch l Med cn Ch a o

This classification may be carried through to biliary cirrhosis as well thus

	Patient C	*Patient D*
Anatomic	Biliary cirrhosis (cholangitic)	Biliary cirrhosis (cholangiolitic)
Etiologic	Post hepatic obstruction (common duct stone)	Post hepatitis
Functional	Group II	Group I

Such a classification is ideal Its habitual use would clarify our thinking and present no special difficulties True enough the question of etiology is not always determinable and exact anatomic classification requires liver biopsy In the latter respect we are more *fortunate than the cardiologist* who cannot obtain a biopsy of the valves or myocardium but this does not discourage the specificity of his diagnosis The most serious objection to this classification is the multiplicity of factors involved in many cases of cirrhosis the various factors acting synergistically Even so the predominant factors may be included under etiology A patient with a chronic valvular deformity may also have dual etiology such as old rheumatic valvular deformity and *atherosclerosis*

Some terms such as juvenile cirrhosis or tropical cirrhosis should be dropped completely since they refer to *nonessential factors* and may dull the observer s zeal for a search for the significant etiologic or anatomic aspects Thus juvenile cirrhosis may be due to congenital syphilis to congenital atresia of the bile ducts (Fig 67a) to hemolytic anemia or to nutritional factors in late childhood Tropical cirrhosis may be due to malnutrition parasitic infestation or other debilitating infections such as malaria or a combination of several of these factors The tropical climate per se certainly has nothing to do with the development of cirrhosis

52 — *Portal Cirrhosis Synonyms, Definition, and Etiology*

SYNONYMS

LAENNEC S cirrhosis alcoholic cirrhosis gin drinker s liver fatty cirrhosis nutritional cirrhosis atrophic cirrhosis periportal cirrhosis hob nail liver

The most acceptable of these terms are Laennec s cirrhosis portal cirrhosis and nutritional cirrhosis While the objection to an eponym in medical nomenclature is as valid here as in other conditions Laennec s name has been firmly rooted in the medical literature since his *description in 1826 of the liver* with yellowish nodules to which he applied the term cirrhosis Indeed the existence of a hard liver with dropsy has been known for over two thousand years before the time of Laennec Portal cirrhosis is a useful term since it refers to an essential pathologic feature while the word nutritional reminds us of the most probable etiologic factor The word alcoholic begs the question since it presupposes that alcohol is the most important etiologic factor a conclusion that is not warranted by the available evidence The term *atrophic is applicable* to many of these livers since they are usually decreased in size in the late stages but since early in the disease there is hepatic enlargement the paradoxical term hypertrophic stage of atrophic cirrhosis has been applied *This is* the stage in which the liver is fatty and deserves the term fatty cirrhosis

Definition

Portal or Laennec cirrhosis is a chronic diffuse usually progressive liver disease etiologically dependent on an agent that produces hepatocellular damage which frequently consists of fatty changes in its incipiency. While the exact etiology remains unknown alcoholism and/or malnutrition is a frequent factor. Clinically impairment of bile excretion is minor while impairment of hepatocellular function is important throughout; splenomegaly, esophageal varices and ascites develop frequently. Pathologically the shrunken coarsely granular or finely nodular liver with the diffuse scarring, pseudolobulation, destruction of normal architecture and nodular regeneration is characteristic. For a comparison with biliary cirrhosis see Table 57.

TABLE 57

Chief Morphological Differences between Portal and Posthepatitic Cirrhosis

	Portal Cirrhosis	Posthepatitic Cirrhosis
Size of nodules	Fine nodules	Large nodules
Fibrous tissue	Fine strands	Broad bands
Inflammatory cells	Polymorphonuclear cells	Monocytic cells

Etiology

Incidence

Cirrhosis is of importance because it is a widespread disease affecting people on all continents and of all races. The group classified as portal or Laennec's cirrhosis is the commonest of all. While it is commonest in Africa and Asia among the Ethiopian and Mongolian races it is a disease to be reckoned with by the Caucasians in both Europe and America. The incidence in different studies varies. The variation may be due to real or artificial causes. Criteria for diagnosis vary; type of population, age, economic status and race of the group will leave an imprint on the final figure. The postmortem incidence may not represent a true picture of the clinical incidence but a clinical study is inferior in accuracy.

In 1931 de Josselin de Jong had available the reports of over half a million autopsies from all over the world with the corresponding incidence of cirrhosis. Laennec's cirrhosis was by far the commonest variety representing 18 to 100% of various groups of cirrhoses. In the majority portal cirrhosis represented over 50% of the cases. The discrepancy about the relative frequency of Laennec's cirrhosis as compared with other varieties is partly attributable to lack of uniform classification; many reports excluded fatty cirrhosis from the Laennec's group, others excluded zooparasitic cirrhosis. Of Karsner 12[illegible] cases, 58 or 47% were of Laennec's cirrhosis; the next most frequent variety was obstructive biliary cirrhosis with [illegible]0 cases or a little over 16%. In a recent report from Chile of 215 cases of cirrhosis 208 were the portal type, 4 toxic and 3 biliary cirrhosis.

The over-all incidence of cirrhosis in autopsy material is [illegible] to 3%. This is borne out by de Josselin de Jong's statistics in which there was an incidence of less than 3% in 463,56[illegible] autopsies and over 3% in 1[illegible],401. Ratnoff and Patek in a review in 19[illegible] found the lowest incidence of portal cirrhosis, 0.43%, in Portland, Oregon, and the highest, 6.95%, in Geneva, Switzerland. In the statistics in which the various types of cirrhoses were considered together the highest incidence was in China, 12.0%. This included those cases with schistosomiasis. Kirshbaum and Shure found 356 cases of portal cirrhosis in 1[illegible],[illegible]67 consecutive autopsies, an incidence of 2.83%. Karsner found an incidence of [illegible]7% but in a later survey found this to be 4%. Hoffman and I[illegible]a found an incidence of death from cirrhosis in less than [illegible]% of 591[illegible] autopsies at the New York City Hospital. In Chile where cirrhosis is frequent it accounts for 1.7% of admissions to the Hospital del Salvador while the autopsy incidence is [illegible]5% (Armas Cruz and co-workers 1951). This demonstrates clearly the discrepancy of incidence between postmortem and clinical observation. It should be conceded that this discrepancy may be in the opposite direction in some statistics.

Age

Portal cirrhosis is a disease of middle and advanced middle age. That the highest in-

cidence of portal cirrhosis is in the age group of 40 to 60 is confirmed by virtually all observers and most of the remaining cases occur after the age of 60 In the Cook County Hospital series over 60% occurred in individuals between 41 and 60 and nearly 22% in those over 61 Karsner found 58% in the 40 to 60 group and an additional 26% in the 61 to 70 year group Ratnoff and Patek found most of their cirrhotics to be between 40 and 64 the average age of Hoffman and Lisa s 93 patients was 54 A recent report from the Mayo Clinic on 444 patients likewise shows the highest incidence in the fifth and sixth decades (Douglas and Snell) This preponderant age distribution is modified a good deal by racial and geographic factors and slightly by sex In the group of cases reported from Chile the highest incidence starts a decade earlier (31–40) and drops off more sharply after 61 so that the highest incidence is in the fourth and fifth decades This earlier age incidence is even more marked among the African and Oriental races In both of these regions of the world life expectancy is much lower and this very common disease occurs in young adults The peak of the incidence in females is about 10 years earlier than in males

Sex

Cirrhosis is commoner in males than in females except in the young groups Cirrhosis under the age of 20 is very uncommon but at that period is commoner in females The ratio of the disease in men as compared with women is 2 1 or higher This ratio was lower in Karsner s series but in Ratnoff and Patek s cases there were 267 males to 119 females in Kirshbaum and Shure s cases 244 males and 112 females in the Chilean group there were 142 men to 66 women The higher incidence in the male has been attributed to the more frequent use of alcohol If this is true the increased use of alcohol by women in the modern era should tend to equalize the ratio between the sexes This could be inferred from the series of 93 cases from New York City which was divided into two groups according to time of occurrence 1920–1934 and 1935–1945 In the former group there were 24 males to 13 females in the latter group an almost equal number of males and females 30 and 26 cases respectively This theory is refuted by the recent Mayo Clinic report which included admissions from 1940 to 1944 with a ratio of males to females of 3 5 1 (Douglas and Snell)

Geographic Distribution

There is a great deal of variation in the incidence of cirrhosis in different parts of the world, this variation does not depend on the climate or locale but on other environmental factors The staggering incidence of 80% among South East African natives has been mentioned (Gilman and Gilman) The incidence is also high in China India and among the native population of the East Indies Miserable diet poor sanitary conditions and widespread infectious diseases are the responsible factors for this high incidence of cirrhosis

Race

That race is not per se responsible for the increased incidence of cirrhosis in the above groups is evident from the fact that there is no such discrepancy in the incidence of cirrhosis between the Caucasian and other races in the United States Although the evidence is not overwhelming and is somewhat contradictory it suggests that cirrhosis is only slightly commoner among American Negroes than among the native Caucasian population This is a far cry from the shocking incidence of cirrhosis among the African natives Moon reported to the International Society for Geographic Pathology that one third of his cases of cirrhosis were in Negroes Ratnoff and Patek reported 3 6% Negroes among their group of cirrhotics as compared with 1 6% Negroes in their control group On the other hand the group from the Cook County Hospital comprised 14% Negroes while of the general hospital population 38% were Negroes However statistics that do not indicate the proportion of Negroes in the population as a whole have little validity

Nationality

There seems to be a higher incidence of cirrhosis among individuals of Italian or Irish

descent in the United States (Ratnoff and Patek) This is corroborated by other observers Richardson found 4 % Italians in a group of 48 patients with cirrhosis in Boston This incidence greatly exceeded the 13% hospital admissions of Italian nationality Rowntree reported the death rate from cirrhosis highest in Italy and lowest in Norway This preponderance in national groups is related to environmental and very likely to dietary habits While increased alcoholic consumption in these groups is an attractive theory it lacks support The per capita alcohol consumption is probably higher in France than in any other country yet the incidence of cirrhosis is not higher there than in the United States Parat and Klotz found a 2 % incidence of cirrhosis in a Latin hospital in females and only 0 53 % in males during the same period This reverse ratio of males to females is unique and is not readily explainable

Heredity and Familial Tendencies

There is no evidence that cirrhosis has hereditary aspects Familial incidence has been reported in special types of cirrhosis (Chapter 73 74) and cirrhosis in adolescence occasionally occurs in siblings Ratnoff and Patek found a brother and sister ages 11 and 12 with cirrhosis and cited several other instances from the literature

Constitutional Factors

Chvastek more than 30 years ago called attention to the frequency of cirrhosis in certain constitutional types In males the disease has been thought to show a predilection for those of the asthenic type with female hair distribution In general the correlation of disease with body structure and other constitutional factors properly belongs in the realm of the art rather than in the science of medicine and usually such conclusions are based on impressions rather than controlled observations Nevertheless I am willing to add my voice to those who claim a constitutional type for this disease I have seen the disease in those with asthenic as well as sthenic habitus but the body hair distribution in the male is frequently unusual I have been impressed with the absence or scantiness of hair on the chest as well as on the abdomen and extremities This corporal alopecia precedes the development of cirrhosis and this disease should be watched for in males with such hair distribution

Occupation

Occupation in itself is of doubtful importance in the etiology of portal cirrhosis however the occupation may introduce some environmental factors which may predicate the development of cirrhosis Although occupational exposure to hepatotoxic agents may result in cirrhosis this is one of the least common causes elicited in patients with this disease Both alcoholism and cirrhosis are commoner in bartenders and those in other occupations related to the selling or distribution of alcoholic beverages In Ratnoff and Patek s series the incidence of these occupations was 49 times that in their control series I have been impressed with the frequency of liver disease in bartenders Laborers also seem to have a higher incidence of cirrhosis than others Rowntree pointed out that cirrhosis is less common in rural areas than in cities reports from the Orient indicate that farmers are commonly afflicted with cirrhosis (Rao 1933 Wang 1936 Suzuki 1934)

Primary Etiologic Factors

1 *Alcohol in the Etiology of Cirrhosis*

So far we have been shooting around our target but not aiming directly at it The factors we are to discuss now are either directly related to the pathogenesis of cirrhosis or have been implicated in this relationship The culprit at which the accusing finger has been pointed for a long time is alcohol Observers have been so impressed with this relationship that it has been incorporated in the nomenclature alcoholic cirrhosis gin drinker s liver beer drinker s liver Is this another *instance* of guilt by association? Is *alcohol the red* herring in portal cirrhosis?

Incidence of alcoholism high in cirrhosis That a history of alcoholic excesses is *frequently* elicited in patients with cirrhosis of the liver is unquestionably demonstrated by the avail

able statistics This is evident from the surveys made in North America and Europe The compiled statistics of Ratnoff and Patek show an incidence of alcoholism of 30 to 86% the lowest figure from Philadelphia and the highest from San Francisco The statistics from Europe are about halfway between these extremes Of the 386 cases surveyed by these workers 54% gave a history of excessive alcoholic consumption Later statistics show approximately the same incidence of alcoholism as shown in the following table from various sources

Incidence of Alcoholism in Cirrhosis

City	Reference	Percentage with Alcoholic History
Chicago	Kirshbaum & Shure 194	41 9%
New York	Ratnoff & Patek 194	54%
New York	Patek 1948	77%
Rochester	Douglass & Snell 1950	64%
Chile	Arma Cruz et al 1951	78%
New York	Hoffman & Lisa 1950	88%

Heavy and moderate alcoholic intake

Incidence of cirrhosis increased after repeal of prohibition In spite of these statistics alcohol remains under suspicion though it is not yet convicted of being a positive factor in the production of cirrhosis The suspicion is heightened by some of the statistics indicating an increase of cirrhosis after repeal of prohibition In the Cook County Hospital series the autopsy incidence of cirrhosis dropped from 2 93% in 1929 to 1 74% in 1932 it rose to 2 60% in 1933 after repeal and continued to climb until 1937 when it reached 4 45% Similar observations were reported from Los Angeles (Evans and Gray) and Philadelphia (Boles and Clark) During prohibition a drop of mortality from cirrhosis from 13 or 14 per 100 000 to 7 per 100 000 was reported by Rowntree

The rapid rise of cirrhosis after repeal of prohibition makes it unlikely that there is a causal relationship since cirrhosis is a chronic disease and would not become manifest in autopsy material for many years Even if the postprohibition increased consumption of alcohol were a factor in the rising incidence of cirrhosis, the likelihood remains that the alcohol displaced food calories from the diet and that the concomitant malnutrition is the important factor

Quantity and type of alcoholic beverage The unqualified statement in a history that a patient consumed inordinate amounts of alcohol is not sufficiently precise to warrant deduction Some reports tried to quantitate this amount of alcohol but by and large the statement of excessive or moderate amounts of alcohol is made It has also been pointed out that when a history of alcoholism is obtained a search is made for liver disease which may not have been discovered otherwise There is no correlation with any specific type of alcoholic beverage wine beer and hard liquors being equally incriminated

Evidence against alcohol as a cause of cirrhosis Even in accepting these statistics we find many individuals—one third to one half—who have cirrhosis without alcoholic excesses This is especially true among female cirrhotics in whom alcoholism is about half as common as among males There are a considerable number of total abstainers who develop cirrhosis This is especially true in India where only 3% have a history of alcoholism as well as in Turkey where religious principles prohibit the use of alcohol As a rule portal cirrhosis in children is seen in the absence of alcoholism although imbibers have been reported even in this group

Also opposed to the etiologic importance of alcohol in the production of cirrhosis is the fact that many reckless consumers of alcoholic beverages fail to develop cirrhosis Many habitual and intermittent alcoholics exhibit only a fatty liver and sometimes even the fatty changes are not marked I have been impressed with the frequency with which chronic alcoholics dying from cerebral injury show a lack of clinical evidence of liver disease and autopsy confirms this discrepancy The incidence of cirrhosis among alcoholics varies widely between 1% and 30% (Ratnoff and Patek) and even in the groups with the higher incidence the majority of alcoholics (70%) escape cirrhosis

The study of the liver by means of liver

function tests in chronic alcoholics has resulted in the conclusion that the nature of the hepatic disturbance differs from the type found in portal cirrhosis There is a lack of evidence from animal experiments where control is more adequate than in human observations that alcohol consumption along with an adequate diet produces cirrhosis (Chapter 41)

In all fairness it must be admitted that the exact status of alcohol in the pathogenesis of Laennec's cirrhosis is uncertain It is not the sole or most important factor however it may be an accessory factor of importance There is no doubt that the diet is neglected by alcoholics and the concomitant malnutrition is of greatest importance It may be that alcohol accelerates the deleterious effects of other agents either by increasing the demand for essential nutrients or by introducing some hitherto unexplained metabolic defect

Nutritional Deficiency

Among the most important contributions to medical knowledge in the past 25 years is the demonstration of the role of malnutrition in liver injury The details of this have been elaborated on in Section VII It may be worth reiterating that this evidence stems from both animal and human observation There is no denial that the cirrhosis of African natives is nutritional in origin The cirrhosis in these patients and in animals under controlled dietary deprivation resemble portal or alcoholic cirrhosis though there may be some dispute about the exact site of origin of the fibrous tissue in experimental cirrhosis (periportal or not) (Chapter 40) The nature of the dietary deficiency which is conducive to the development of liver injury is as follows

1 Protein deficiency
   a deficiency of sulfur-containing amino acid
   b deficiency of lipotropic factor
2 Carbohydrate deficiency
   which may act by increasing the demand of proteins and
3 Excess of fats
   which may act by
   a increasing the need for lipotropic agents
   b increasing the susceptibility of the liver to exogenous toxins
4 Deficiency of vitamins
   a vitamin E
   b B complex
   c ascorbic acid (?)

While the evidence of nutritional deficiency as the etiologic agent in cirrhosis is incontrovertible in certain geographic areas the evidence is neither clear nor unmistakable in the run of the mill cirrhoses in North America and in European countries Obtaining an accurate nutritional history is beset with difficulties and pitfalls Several observers have attempted to determine the incidence of nutritional deficiency in cirrhosis and found it to be considerable In Ratnoff and Patek's group there were only 17% with definite evidence of nutritional deficiency while the recent (1948) study by Patek and co workers showed an incidence of 73% The recent study by Douglass and Snell showed only 34% with an obviously deficient diet but their 64% with alcoholism admittedly included many with dietary deficiency The statistics of the Chilean workers (Armas Cruz and associates) are most revealing in this respect Only 36% of their patients had a normal nutritional history while 64% were on either a moderately or a markedly deficient diet In a similar group of noncirrhotics these figures were reversed (65% gave a history of normal nutrition

I have been in the habit for many years of questioning patients with liver disease about their nutritional habits and have found many with a distaste for high grade proteins such as beef and a greater interest in fat and meats with a high fat content such as pork Regardless of the approach to the problem of etiology there still remains a considerable group of patients who are neither alcoholic nor obviously malnourished The recent Mayo Clinic study of cirrhotics showed no apparent etiologic agent in one out of five (19.6%) Other etiologic factors are undoubtedly contributory among these are toxins and various infections to be discussed forthwith but some obscure and hitherto undetermined factor must be involved in this considerable group of patients in whom no known etiologic factor is detect

able This obscure factor may be responsible for the development of cirrhosis in one patient and its absence may account for the freedom from this disease in another patient with an identical alcoholic and nutritional history

3 *Antecedent Jaundice and Hepatitis*

With the increase of the epidemic and homologous serum variety of hepatitis and the demonstration that it can lead to chronic hepatic disease interest has been aroused in the possibility that this acute disease may eventuate in portal cirrhosis There is lack of agreement on the question of whether acute hepatitis can terminate in portal cirrhosis In this country doubt has been expressed about this metamorphosis (Patek 1951) while in England this is considered to be a likely transformation (Sherlock) I know from personal experience that a biopsy may be reported as showing portal cirrhosis and subsequently at autopsy may show typical morphology of post *necrotic cirrhosis (see Case 6 Figure 47)* Therefore statistics of portal cirrhosis arising from viral hepatitis must be accepted with caution unless autopsy material is available

Deductions based on the incidence of antecedent jaundice or blood transfusions can be accepted only as presumptive and not conclusive evidence A history of blood transfusions in only 2 of 284 patients from the Mayo Clinic group is apropos Even if it were assumed that both of these patients had developed serum hepatitis one would have to assume further that both developed chronic hepatitis and with both these improbable assumptions blood *transfusions could be considered causative in* less than one half of one per cent

Much has b en made of a history of antecedent jaundice However even if such history were dependable which it frequently is not unless supported by medical affidavit it may mark the origin of cirrhosis rather than the *onset of acute hepatitis* Also the jaundice may be caused by an exogenous toxin to which the patient was exposed at the time A history of jaundice was given by -5 or 6 5%, of Ratnoff and Patek s group anywhere from one to 36 years prior to the *manifestation of cirrhosis* A history of jaundice has been obtained by students of cirrhosis prior to the time of this report some *of these were attributed to catarrhal jaundice* (Eppinger, 19 5) while others were more cautious in its interpretation (Bloomfield 1938)

A more recent observation along this line is the history of antecedent jaundice in ,6% of the Mayo cases this figure is considerably *lower than the ones previously mentioned* Patek and co workers (1948) found a history of jaundice in 4% of their patients

The study by Howard and Watson is of particular interest The 100 patients with cirrhosis analyzed by the Minnesota workers shows the very high incidence of antecedent *jaundice of 33% and more than one half of* these or 17% had a clear cut history of infectious hepatitis This incidence of hepatitis is raised to 18% by the exclusion of some doubtful cases of cirrhosis This material is of further interest since the incidence of alcoholism was quite low only -5% for the entire *group Only - or 6% of the female patients* had a history of alcoholism while -7% had a history of hepatitis These workers point out that there may be a reciprocal relationship between alcoholism and hepatitis with their series showing a preponderance of viral etiology

One hundred control patients gave a history of jaundice in 7% and hepatitis in 3% but in half of these records there was no evidence of inquiry about jaundice This would weight the statistics in the cirrhotics since a patient with proved or suspected liver di ease would always be interrogated about this symptom The significance of their observations is further diluted by the fact that 5 of the 14 cases of ci rho es were of the cholangiolitic type *Neverthel s* these observations are unique in calling attention to the possible importance of *hepatiti in* the genesis of portal cirrhosi

The study of Armas Cruz and a *sociates* does not add emphasis to the importance of hepatitis as a cause of portal cirrhosis *While* they elicited a history of jaundice *and poss ble* hepatitis in 25 7% of their cirrhotics the *non* cirrhotic control group gave such a h s ory in 28 3% *of ca e* This difference is of questionable statistical significance

In conclusion, it may be stated that at the present time viral hepatitis must be considered a possible precursor of a type of cirrhosis undistinguishable in the later stages from portal cirrhosis. It contributes only a relatively small number of cases to the entire pool of portal cirrhosis. This question could be settled by a careful follow-up of the large number of cases seen in the armed forces and any other large group *that would be suitable for intensive* statistical study and long-range follow-up.

4. Exposure to Chemical Toxins

The effect of various chemical toxins on the liver is elaborated upon in Section V, page 152. If the exposures are sublethal, repeated and prolonged, chronic liver injury and fibrosis result. Acute exposure to most toxins results in widespread parenchymal necrosis. This should lead to postnecrotic cirrhosis, but as in the case of hepatitis, the chronic lesion may have all the characteristics of portal cirrhosis.

The *toxins that are most likely to be in*volved in cirrhosis are arsenic, carbon tetrachloride (Case 3, page 161), cinchophen, phosphorus, chloroform and the chlorinated hydrocarbons. There are several points that must be kept in mind in evaluating the role of toxin in the production of cirrhosis. A history of exposure to some toxic agent is no proof that the toxin was present in sufficient concentration or for a sufficiently long period of time to produce the deleterious results. Exposure to cinchophen, with its unpredictable effect on the liver, can be regarded as a conjectural cause of cirrhosis (Chapter [illegible]4, page 171). In general, a history of jaundice at the time of exposure to a toxin makes it very likely that liver damage from that particular agent occurred. A history of exposure to toxins can be accepted as presumptive evidence of a causal relationship. Exposure to alcohol accentuates the toxic effect of certain poisons, such as carbon tetrachloride. Dietary deficiency makes the liver more susceptible to hepatotoxic agents.

Frequent use of inorganic arsenic, such as Fowler's solution, can produce portal cirrhosis (page 166). Its incorporation into an asthma medicine has been recently reported as resulting in hepatic cirrhosis. The accompanying skin lesions should call attention to the correct etiologic agent. The occurrence of jaundice or cirrhosis in a patient exposed to arsphenamines brings up two other potential causes of hepatotoxicity: viral hepatitis (from needle) and syphilis. These relationships are fully discussed in the appropriate sections (Chapters 37, 38, [illegible]4).

The possibility of implicating a definite *toxin in the etiology of portal cirrhosis* is numerically unimportant, since few patients give such a history. The only exception to this is the history of syphilis with arsenical therapy. Thirty-six of Ratnoff and Patek's patients were exposed to some form of arsenic. Of Douglas and Snell's patients, only three gave a history of injections of arsenic and one was exposed to carbon tetrachloride. I have seen an occasional patient with cirrhosis who gave a history of cinchophen medication many years before. It may be concluded that, while an occasional patient with cirrhosis gives a history of exposure to a known toxin which may be of importance in the causation of the disease, in the majority of cases such history is unobtainable.

5. Infectious Agents

a. Syphilis. A history of syphilis is *not in*frequently elicited in patients with portal cirrhosis. Such a history was obtained in [illegible]% of Evans and Gray's cases, in 16% of Ratnoff and Patek's cases and in 8% of the recent series from the Mayo Clinic. The problem of the nature of the liver damage in syphilis is discussed in detail in Chapter [illegible]. Probably *only in congenital hepatic syphilis can this* infection produce changes akin to portal cirrhosis. Therefore, in the juvenile group, portal cirrhosis may be truly syphilitic in origin. Except for this particular type of cirrhosis, syphilis may contribute to development of portal cirrhosis in the following ways: (1) the use of hepatotoxic agents in the treatment of syphilis (Chapter [illegible]4); (2) increased incidence of viral hepatitis of needle origin, and (3) the *greater coincidence of alcoholism in persons* exposed to syphilis. The objections to these explanations lie in the fact that some of the patients with a history of syphilis were untreated, and a history of syphilis is frequently

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obtained in patients with cirrhosis in countries where alcoholism is not a factor Both in Syria (Yenikomshian) and in India (Rao) syphilis is a frequent accompaniment of cirrhosis

b Malaria Malaria is another disease that has been associated with cirrhosis This association is primarily due to the fact that in many tropical areas both diseases are very common As was discussed in Chapter 33 malaria even more so than other infectious diseases can produce liver damage and when this infection is associated with malnutrition the soil is fertile for development of cirrhosis Thus in a group of cases studied in India 84% of cirrhotic had a history of malaria However in these areas the incidence of malaria in the general population may be nearly that high and therefore would not be valid evidence of causal relationship

Malaria was elicited in the history of 33 patients or 9% of the Ratnoff and Patek series A series of cases from the Mayo Clinic reported in 1931 (Chapman and co workers) showed an incidence of malaria of 11% while in the more recent series 1950 malaria is not even mentioned as an etiologic agent As pointed out in Chapter 33 malaria can produce serious and extensive liver damage but the evidence points to a prompt restitution of the liver after recovery In tropical areas where a patient may remain infected for many years or become reinfected numerous times the likelihood of permanent liver damage is greater

c Parasitic infections The effect of various metazoa on the liver and particularly the blood flukes (Schistosoma) and the liver flukes (Clonorchis) is discussed in Chapter 34 Their occurrence in the liver of Orientals dying from cirrhosis is very high and the cirrhosis found in these individuals has been classified as zooparasitic cirrhosis Some doubt has been expressed that these parasites by themselves can produce true portal cirrhosis (Chapter 34) The concomitant malnutrition may be the salient causal factor

d Other infectious diseases Any infection or febrile illness may produce liver injury (Section VI) But other specific diseases have been implicated in the pathogenesis of cirrhosi This is especially true about the enteric in fections such as the dysenteries and typhoi fever as well as tuberculosis These disease like malaria are common in the regions of th world where sanitation is primitive and th diet is inadequate Their frequent concurrenc in patients with cirrhosis may be regarded a coincidental rather than causal However an infection may act synergistically with anothe hepatotoxic agent in accelerating and pro longing liver damage Undulant fever with it widespread granulomatous involvement of th liver should be watched as a potential caus of portal cirrhosis There is as yet no data to support suspicion that this infection is th cause of cirrhosis except in rare instances

Conclusions about Etiology of Portal Cirrhosis

This lengthy discussion may leave the reader bewildered about the cause of portal cirrhosis Several points require re emphasis (1) The etiology of portal cirrhosis as we know it in North America or Europe has not been completely and satisfactorily elucidated ( ) fully developed portal cirrhosis is probably the sum total of various noxious agents that made their imprint on the liver throughout the life of the patient (3) the etiologic factors which appear acceptable with the evidence at hand in the order of their importance are

- a Dietary deficiency
- b Alcoholism probably related to dietary deficiency
- c Viral hepatitis
- d Toxins carbon tetrachloride arsenic chloroform phosphorus, etc
- e Infections of various types

Portal Cirrhosis—Summary

Etiology

Incidence

2 to 3% of autopsy material
variations 0 43% to 12%

Age

40 60 highest incidence (North America and Europe)
30-40 in African and Asiatic people

Peak incidence 10 years earlier in female

Sex

Ratio of males to females 2 1 or higher

Geographic distribution

South East African natives, 80% incidence

China India East India also high

Race

Negroes in the U S.A have slightly higher incidence than white population

Nationality

Italian and Irish show highest incidence

Heredity and familial factors

Not important

Constitutional factors

Asthenic habitus

Female hair distribution

Occupation

Bartenders and various handlers of intoxicating beverages

Laborers

Farmers in Orient

Occupation entailing exposure to hepatotoxic agents

Primary Etiologic Factors

1 Alcohol

Evidence favoring alcohol as cause of cirrhosis

a Incidence of alcoholism over 50% (30 to 88%)

b Cirrhosis decreased during prohibition and increased after repeal

c Decreased mortality 13 14/100 000 to 7 100 000 during prohibition

d Quantity of alcohol consumed not easily determinable

e Type of beverage does not determine development of cirrhosis

Evidence against alcohol as cause of cirrhosis

a One half to one third of patients with cirrhosis do not have history of alcoholism

b Females have much lower (about one half incidence of alcoholism)

c Total abstainers develop cirrhosis

d Cirrhosis common in India and Turkey where alcohol is prohibited

e Childhood cirrhosis—rare implication of alcohol

f Many alcoholics do not develop cirrhosis (70 to 99%)

g Liver function tests in chronic alcoholics differ from those seen in cirrhosis

h Animal experiments do not support the cirrhotigenic effect of alcohol

Alcohol acts by conditioning malnutrition and by introducing a metabolic defect which accentuates other noxious agents

2 Nutritional deficiency Conclusive proof of cirrhosis resulting from dietary deficiency from animal and clinical observations

a Protein deficiency foremost

b Carbohydrate deficiency secondary role

c Fat excess may accentuate protein deficiency and synergize the effect of toxins

d Vitamin deficiency

History of deficient diet was high as 73% of some groups of cirrhotics

3 Antecedent hepatitis and jaundice

Hepatitis is accepted and rejected as a cause of portal cirrhosis by different workers

About 5% of cirrhotics give a history of antecedent jaundice or hepatitis

4 Exposure to chemical toxins

Exposure must be prolonged and repeated to sufficient concentration

Toxins most frequently involved

Arsenic

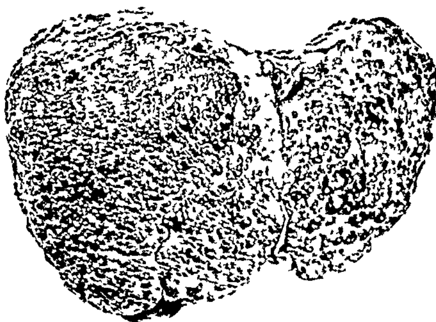
Carbon tetrachloride

Phosphorus

Chloroform

Cinchophen

Alcohol and dietary deficiency exaggerate effect of toxins



F g 68 Ph g aph of the l er of a pa ent w th po t l c rh Th p t ent r h gh f er f four months pr o r dea h f om l ver f lure Ther w s no nfect on t account for the fe r

are l ghter gray in color becaus of the h gher proport on of fibrous t ssue Redd sh yellow or orange s th class cal color of portal c rrhos s Th s may be nterspersed w th green when cterus s marked

The surface s nodular These nodules are usually small and regular n contrad st nct on to the mass ve nodules of postnecrotic c rrhos s (F gure 68) The nodules are usually several m ll meters n d ameter but may be even less than 1 mm The nodules represent or g nal parenchyma encompas ed w th fibrous t sue or reg nerating hepat c t ssue In the early stage when fatty metamorphos s rather than the fibros s s most prom nent the surface may be me ely granular and not nodular

pleen

Th s organ unl ke the l ver s almost un formly enlarged The average we ght of 11 spleens n Ratnoff and Patek s s r es was 4 0 gm w th a var a t on of 30 to 1 00 gm Th s nd cates that occa s onally a small spleen s encountered All but of the 341 spleens n K rshbaum and Shure s ser es were enlarged The largest spleen n th s ser es we ghed 045 gm There were 76 spleens that we ghed 400 to 600 gm th s was the largest group The Ch cago o kers n t ced that Negroes w th c rrhos s are l kely to have smaller spleens poss bly because of concom tant s ckle cell anem a Hoffman and L st found the average we ght of the spleen to be 33 gm and 307 gm n the two chronolog cal groups The r small group seemed to nd cate that n the last per od 1935 1945 the spleens were decreased n s ze (307 gm) wh le the average s ze of the l ver ncreased from 1324 to 798 gm In the ser es from Ch le 68% of the spleens were enlarged The poor correlat on bet veen the patholog cal and cl n cal data of l ver and spleen s ze w ll be d scussed under the cl n cal features

Esophageal Varices

Esophageal var ces may be m ssed on rout ne postmortem exam nat on and therefore the autopsy nc dence may be lower than ts cl n cal nc dence These d lated ve ns wh ch may be qu te prom nent on esophagoscopy or x ray exam nat on may be obscure on gross nspect on post mortem because they are ollapsed and h dden by the overly ng mucosa Careful m croscop c exam nation of the term nal esophagus would undoubtedly reveal some that are m ssed on gross nspect on It s not at all uncommon to see a pat ent w th c rrhos s d e from upper gastro ntest nal h morrhag and at autopsy

5 Infectious Agents
  a Syphilis
    History of syphilis in about 10% of cases
    In 'juvenile' cirrhosis, syphilis may be a direct factor
    In adults syphilis may act by
      (1) increased exposure to hepatotoxic agents
      (2) increased incidence of viral hepatitis
      (3) greater likelihood of alcoholism
  b Malaria
    Coexistence of malaria and cirrhosis very high in tropical areas (India 84% have malaria)
    Malaria causes liver damage
    Malnutrition is accentuated by the infection
  c Parasitic infections
    Schistosomiasis
    Clonorchiasis
  d Other infections
    Infections of any type may produce hepatic injury and may act synergistically with other hepatotoxic agents
    Infectious diseases to be watched because of frequent association or specific changes in liver are
      (1) bacterial dysenteries
      (2) typhoid fever
      (3) tuberculosis
      (4) undulant fever

53

Pathology of Portal Cirrhosis, Structure of the Normal Liver

Gross Pathology

Liver

The size of the liver is of considerable interest because of the frequent lack of correlation between the clinical and the pathologic findings and because of the occasionally used synonym atrophic cirrhosis This term implies a small shrunken liver and distinguishes it from the hypertrophic (biliary cirrhosis) But the liver in this disease is not always small hence the awkward terminology of hypertrophic stage of atrophic cirrhosis

While the liver is usually smaller than normal it may show wide variations in size and weigh 500 o 5000 gm (Karsner) Over half of the livers in this disease are lighter than normal Thus in 118 cases reported by Roberts 71 weighed less than 1600 gm Forty three of 78 livers analyzed by Ratnoff and Patek weighed less than 1800 gm In the Cook County series 1 9 livers out of 343 weighed less than 1500 gm The series from Los Angeles County Hospital showed 111 livers of the total of 77 under 1500 gm (Evans and Gray) Karsner s 58 livers showed 8 livers less than 1500 gm in weight Armas Cruz and co workers found at autopsy livers decreased in size in 55% and increased in size in 34% the remainder were normal in size

The very large livers are extremely rare Karsner has seen only one liver weighing 3500 gm In the cases reported by Kirschbaum and Shure 36 livers weighed over 3000 gm In Ratnoff and Patek s series there was one liver that weighed 5100 gm

The color and consistency of the liver varies with its size The larger livers are likely to be softer and greasy in appearance because of the higher fat content or more reddish in appearance because of the greater vascularity and more regeneration The small livers are harder cut with a grating sound and



F g 68 I hotograph of the l r of a patient with port l rrh s Th s patient ran high fe e f r four month p r to de th fr m l r f ilu e Th re wa n) infect on t acco nt for the fever

are lighter gray in color because of the h gher proportion of fibrous tissue Reddish yellow or orange is the classical color of portal cirrhosis This may be interspersed with green when icterus is marked

The surface is nodular These nodules are usually small and regular in contrad stinction to the massive nodules of postnecrotic cirrhosis (Figure 68) The nodules are usually several millimeters in diameter but may be even less than 1 mm The nodules represent original parenchyma encompassed with fibrous tissue or regenerating hepatic tissue In the early stage when fatty metamorphosis rather than th fibrosis is most prominent the surface may be merely granular and not nodular

Spleen

This organ unlike the liver is almost uniformly enlarged The average we ght of 111 spleens in Ratnoff and Patek s series was 4 0 gm with a variation of 30 to 1700 gm This indicates that occasionally a small spleen is encountered All but 12 of the 351 spleens in Kirshbaum and Shure s series were enlarged The largest spleen in this series weighed 045 gm There were 76 spleens that weighed 400 to 600 gm this was the largest group The Chicago workers noticed that Negroes with cirrhosis are likely to have smaller spleens possibly because of concomitant sickle cell anemia Hoffman and Lisa found the average weight of the spleen to be 33 gm and 307 gm in the two chronological groups Their small group seemed to indicate that in the last period 1935 1945 the spleens were decreased in size (307 gm) while the average size of the liver increased from 1 4 to 1798 gm In the series from Chile 68% of the spleens were enlarged The poor correlation between the patholog cal and clinical data of liver and spleen size will be discussed under the clinical features

Esophageal Varices

Esophageal varices may be mis ed on routine postmortem examination and therefore the autopsy incidence may be lower than its clinical incidence These dilated veins which may b quite prominent on esophagoscopy or x ray examinat on may be obscure on gross inspection post mor em because they are collapsed and hidden by the overlying mucosa Careful microscopic examination of the terminal esophagus would undoubtedly reveal some that are missed on gross insp ction It is not at all uncommon to see a patient with cirrhosis die from upper gastrointestinal hemorrhag and at autopsy

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    History of syphilis in about 10% of cases
    In "juvenile" cirrhosis, syphilis may be a direct factor
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53 — *Pathology of Portal Cirrhosis, Structure of the Normal Liver*

Gross Pathology

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cells of the limiting plate are continuous with the intralobular plates of cells In the normal human liver all the liver cell plates are one cell thick

Small venules arising from the portal vein tributaries penetrate the limiting plate and on the other side of the limiting plate ramify to form sinusoids The sinusoids are deviated toward and empty into the central vein The central veins in turn empty almost perpendicularly into a sublobular vein which is a tributary of the hepatic vein The sinusoids also receive blood from arterial capillaries branches of the hepatic artery which penetrate the limiting plate Some of the arterial branches flow into the sinusoid at the periphery of the lobule and adjacent to the limiting plate of the portal canal and others empty into sinusoids closer to the center of the lobule near the central vein These arterioles or arterial capillaries have sphincteri activity and therefore can vary the blood flowing out of them

Bile capillaries or canaliculi make a polygonal network between adjacent liver cells They seem to have a wall of their own This network of bile capillaries can be seen in a tangential section of a liver plate (lamina) In cross sections the bile capillaries are seen as dots between the hepatic cells These capillaries flow into an intralobular ductule and thence into an interlobular collecting bile ductule which carries the bile to a portal bile duct The intermediate ducts which connect the intralobular bile ducts with the interlobular bile ducts are referred to as the canals of Hering

The perisinusoidal tissue spaces communicate with the periportal tissue space known as the space of Mall The communication is through the channels formed through the limiting plate (lamina) by the vascular channels which pierce it There seems to be no direct communication between the space of Mall and the lymph ducts

A meshwork of fine reticulum fibers permeates the entire organ and forms the framework around which the more important structures are disposed These supporting structures are so sparse as to be invisible in the ordinary sections except in the periphery of the lobule and in the portal spaces Even the interlobular connective tissue is normally very sparse For adequate visualization of the intralobular and perilobular reticulum structures special preparations and staining techniques are required This concept of the structure of the liver is depicted in Fig 69

This background of the structure of the normal liver is necessary for the clear understanding of the morphological changes that take place in cirrhosis

Structure of the Normal Liver—Summary

Liver cells arranged in irregular walls—hepatic laminae

Spaces between hepatic laminae hepatic lacunae

Interconnected hepatic lacunae—hepatic labyrinth

Hepatic labyrinth consists of channels through which intrahepatic blood lymph and bile flow

Portal canals—tunnels through liver parenchyma which houses

1 branch of hepatic artery

2 branch of portal vein

3 several bile ducts

4 lymphatics

5 nerves

Enmeshed in connective tissue and surrounded by tube of hepatic cells—portal limiting plate—lamina limitans

Small venules from portal vein tributaries—penetrate the limiting plate and give rise to sinusoids flow toward and empty into central vein

Central vein empties perpendicularly into sublobular vein tributary of hepatic vein

Branches of hepatic artery also penetrate limiting plate and empty into sinusoids either at periphery or closer to center of lobule

Bile capillaries have wall of their own form polygonal network between adjacent liver cells

Flow into

Intralobular ductules these flow into

Interlobular collecting ductules and then into a

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Structure of the Normal Liver—Summary

Liver cells arranged in irregular walls hepatic laminae

Spaces between hepatic laminae hepatic lacunae

Interconnected hepatic lacunae hepatic labyrinth

Hepatic labyrinth consists of channels through which intrahepatic blood lymph and bile flow

Portal canals tunnels through liver parenchyma which houses

1. **branch of hepatic artery**
2. **branch of portal vein**
3. **several bile ducts**
4. **lymphatics**
5. **nerves**

Enmeshed in connective tissue and surrounded by tube of hepatic cells—portal limiting plate lamina limitans

Small venules from portal vein tributaries penetrate the limiting plate and give rise to sinusoids flow toward and empty into central vein

Central vein empties perpendicularly into sublobular vein tributary of hepatic vein

Branches of hepatic artery also penetrate limiting plate and empty into sinusoids either at periphery or closer to center of lobule

Bile capillaries have wall of their own form polygonal network between adjacent liver cells

Flow into

Intralobular ductules these flow into

Interlobular collecting ductules and then into a

Portal bile duct
Canals of Hering are the connections between the intralobular and interlobular bile ducts
Space of Mall is the periportal tissue space it communicates with the perisinusoidal tissue spaces
Reticulum meshwork which is very fine, permeates the entire organ

MICROSCOPIC PATHOLOGY

Histogenesis

The manner in which the profound histological changes develop in a patient with advanced cirrhosis is of more than academic interest for it not only may be a clue to etiology but may point the way to therapy and help to explain some of the clinical complications

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FIG 69 MORPHOLOGY OF THE HUMAN LIVER (Description of Stereogram by Hans Elias Ph D Department of Anatomy Chicago Medical School reprinted from *The Liver Lobule* published by G D Searle & Co) *The liver is a continuous mass of hepatic cells* The e are arranged in the form of liver plates (laminae hepatis) which form the walls of spaces called hepatic lacunae (1) Through *perforations in the liver plates the lacunae are connected with each other and form the hepatic labyrinth* The hepatic lobules are ill defined areas which surround the central veins (a b c d) and are continuous with one another

The continuous liver parenchyma is tunneled by portal canals (3 center of illustration) which are surrounded by a continuous sheet of hepatic cells the periportal limiting plate (4) The limiting plate is continuous with the intralobular plates Each portal canal contains a branch of the portal vein (5) a branch of the hepatic artery (6) a network of bile ducts (7) a network of lymph vessels (8) and nerves Since these nerves are as yet undescribed they are not shown in the stereogram

All the e structures are held together by the periportal connective tissue (9) From the portal vein inlet venules (10) *penetrate through holes in the limiting plate On the other side of the limiting plate* it ramifies into sinusoids (11) which are suspended in the lacunae and empty individually into the central veins (a)

The central veins (a b c d) unite almost perpendicularly with a sublobular vein (1) a tributary of a hepatic vein The sublobular and larger hepatic veins are surrounded by the perihepatic limiting plates

From the hepatic artery (6) arterial capillaries and arterioles enter the lobules at two (perhaps three) *different levels There is some evidence that one set of arterial capillaries empties into peri*portal sinusoids (6a) and it is certain that another set of arterial capillaries (6b) empties into the sinusoids near the center of the lobules Recent unpublished experiments indicate that a third set of arterial capillaries supply the intermediate zones of the lobules Each set of arterial capillaries has sphincters Prolonged contraction of one or the other set of sphincters may contribute to zonal pathology by causing zonal anoxia

In most instances the central and sublobular veins are at right or oblique angles to the portal canals *parallel direction (2c) is rare The spaces between the walls of the sinusoid and the liver* plates (13) are the perisinusoidal spaces of Disse At the places at which the limiting plate is pierced by an inlet venule the perisinusoidal spaces are continuous with the periportal tissue space of Mall (14) From here the biliary fluid seeps through the periportal connective tissue (9) into the lymphatics (8)

A liver plate is shown in tangential section (15) The bile capillaries a e seen forming a polygonal network within the liver plates between hepatic cells In those plates (on the right side of the stereogram) which are cut vertically the cross sections of bile canaliculi are shown as dots between the cells The bile canaliculi have a solid wall of their own This accounts for their occasional presence along the free surfaces of the hepatic plates (16)

Minute bile ducts (17) enter the lobules and receive bile from intralobular plates The bile ducts never end freely they always form loops or networks Most of the bile drains through the canalicular network in the limiting plates and from here through the canals of Hering (18) into the network of bile ducts

(*This stereogram is based on data from the following publications* by Hans Elias Revision der Struktur der Saugerleber Anat Anz *96* 454 (Dec *1*) 1948 Beobachtungen uber den Bau der Saugerleber Anat Nachr *1* 8 1949 A Re Examination of the Structure of the Mammalian Liver I Parenchymal Architecture Am J Anat *84* 311 (March) 1949 The Liver Cord Concept After One Hundred Years Science *110* 470 (Nov 10) 1949 A Re Examination of the Structure of the Mammalian Liver II The Hepatic Lobule and Its Relation to the Vascular and Biliary Systems Am J Anat *85* 379 (Nov) 1949)

such as portal hypertension and ascites There are four histogenetic factors in the production of the morphologic changes

1 fatty metamorphosis
2 the site of origin of the fibrous tissue
3 the role of the regenerating nodules and
4 the intrahepatic circulatory alterations and their causes

Fatty metamorphosis Fatty changes uniformly precede certain types of nutritional cirrhosis (Chapter 40) and are frequently seen in various stages of human portal cirrhosis There is a reciprocal relationship between the quantity of fat in the liver and the extent of the fibrosis This relationship between fat and fibrosis was noted by us in nutritional cirrhosis in guinea pigs and rabbits and has also been noted in human cirrhosis The term fatty cirrhosis calls attention to the fatty metamorphosis in portal cirrhosis which is usually nutritional in etiology The so called hypertrophic stage of atrophic (portal) cirrhosis represents an early stage of the cirrhotic process and the large liver is filled with fat There is therefore indication in the human disease that fatty changes precede the stage of marked scarring

The question whether the fatty metamorphosis is instrumental in causing fibrosis is by no means settled This causal relationship is disputed by some English observers It seems to me that most experimental and clinical data support such causal relationship Moschcowitz is emphatic in his insistence that fatty changes are invariable precursors of portal cirrhosis He does not define how the fatty changes lead to fibrosis but indicates that the fatty liver is always accompanied by periportal round cell infiltration and this exudative process is followed by new capillary formation and fibrous tissue formation The fatty liver produced experimentally by deficiency of lipotropic factors leads to overdistention of parenchymal cells with fat and eventual rupture of the cell membrane and the formation of fatty cysts (lipodiastemata) The formation of these cysts may result in destruction of some cells by mechanical means and compression of the cell membranes and the adjacent reticulum so that when the cysts empty strands of fibrous tissue are left Likewise these fat distended cells may compress the vascular channels with resultant ischemia cell atrophy or necrosis and final replacement with fibrous tissue As is pointed out in Chapter 40 there is some disagreement as to the site of origin of the fibrous tissue in experimental nutritional cirrhosis But as we shall see later the nonportal origin of the fibrous tissue is not a valid argument against the pathogenesis of Laennec's cirrhosis in this fashion

Site of origin of fibrous tissue The precise site of origin of the fibrous tissue is difficult to determine in fully developed cirrhosis It has been pointed out that while fully developed nutritional cirrhosis due to deficiency of lipotropic factors has the appearance of predominately periportal distribution of fibrosis there is some evidence that the fibrous tissue actually originates in the central portion of the lobule In advanced cardiac cirrhosis the final distribution of the fibrous tissue may be predominantly portal yet its origin is unquestionably centrolobular

The elucidation of this problem is complicated by the lack of precise knowledge of the factor or factors directly responsible for the fibrosis In some situations necrosis of liver cells is followed by collapse of reticulum fibers and finally by proliferation of newly formed fibrous tissue This is probably the case in cardiac cirrhosis and postnecrotic cirrhosis In these instances one needs only to localize the area of necrosis to decide where the fibrous tissue will start In portal cirrhosis there is no evidence that frank necrosis is the precursor of fibrosis If fatty metamorphosis per se were the precursor the area of its most advanced development should be the site of origin of the fibrous tissue In some animal experiments and to a lesser extent in man the fatty changes are most marked in the centrolobular area therefore one would expect the fibrous tissue to originate there

Moschcowitz while emphasizing the importance of fatty changes in cirrhosis turns to the periportal exudative process for the source of the fibrous tissue He insists that fibroblastic proliferation originates in the region of and probably from these inflammatory cells

are not distorted and compressed like the areas adjacent to hyperplastic nodules It has been suggested by some that the regenerating nodules are supplied mostly by arterial blood These vessels having a higher hydrostatic pressure are able to resist the encroachment of the growing tissue for a longer period of time When the arterial pressure falls or the pressure of the nodule exceeds the blood pressure within these arterioles necrosis ensues with consequent liver failure If this sequence of events is correct it is difficult to see how arterial ligation can do anything but harm in the treatment of portal cirrhosis

The reconstructions of Elias likewise demonstrate the impingement of the rapidly growing nodules upon tributaries of the hepatic veins while the portal veins are not encroached upon This observer claims that these nodules are supplied by blood from the arterial as well as portal venous capillaries The flattening of the adjacent hepatic vein causes stasis in the center of the nodule with resultant cellular necrosis (Fig 70)

It can be seen from the foregoing description that regeneration rather than fibrosis may result in portal hypertension and that the portal hypertension may result from impingement on the hepatic veins and hence produce an intrahepatic Chiari s syndrome (p 3-7) Likewise this pathogenesis of portal hypertension would explain the cases with esophageal varices and hemorrhage that show good hepatic function however it would fail to explain the collateral esophageal circulation in other patients with fibrosis but little or no evidence of regenerating nodules

Intrahepatic shunts In addition to the impingement of regenerating nodules and fibrous tissue on the venous channels other intrahepatic vascular changes occur The increased arteriovenous anastomosis pointed out by McIndoe has been mentioned (Chapter 49) These factors would tend to increase the portal pressure or slow the circulation or both Daniel and co workers showed that the fibrosis resulted in a rise in portal pressure but slowing of circulation did not occur until the remaining intact venous channels could no longer handle the added burden Macroscopic nodular cirrhosis distorted the angiographic picture of the liver and increased the resistance to perfusion Bradley and associates (1952) demonstrated that hepatic flow is decreased in human cirrhosis A compensatory mechanism appears to develop which may tend to operate in the opposite direction that is to speed the blood flow and reduce the portal pressure As destruction of hepatic cords occur sinusoids collaspe and new capillary channels are formed these widen and form a direct communication between the portal and hepatic vein radicals In other words an internal Eck fistula or portacaval shunt is formed (Popper Elias and Petty Moschcowitz) Practically apparently this shunt does not appear to improve the circulatory derangement or reduce the portal hypertension

The intrahepatic vascular channels may on rare occasions undergo marked changes and represent an unusual form of cirrhosis An abundance of interlacing blood filled sinusoids give the liver an angiomatous appearance Ricketts and Green reported a liver showing such angiomatous changes and cited six similar cases in the literature It is possible that some vascular abnormality preceded the development of cirrhosis

Histopathology

The microscopic features of portal cirrhosis can be subdivided into the following categories

1 fibrosis
2 necrosis and degeneration
3 nodular hyperplasia
4 bile duct multiplication and
5 inflammatory cell infiltration

1 *Fibrosis* We will discuss this first because of its close association with cirrhosis and because it is the most conspicuous histologic change There is complete distortion of the normal liver architecture consisting of the relationship of the liver lobule to the central vein and to portal space This thorough and widespread alteration of the liver architecture involving all the lobes is a characteristic feature of portal cirrhosis The fibrous bands vary in size but they are usually narrow and fine unlike the coarser and thicker bands in post necrotic cirrhosis (Fig 71) The areas of parenchymal cells that are surrounded by fibrous bands are usually small smaller than a normal

lobule and even if the areas are larger the normal lobular structure with a central vein is lost

The quantity of fibrous tissue in the cirrhotic liver varies a good deal It has already been mentioned that in some cirrhotic livers there may be no marked increase in fibrous tissue but the increase may be apparent because of the collapse of the pre existing reticulum framework In this connection the work of Warren and Wahli is of interest These workers measured the fibrous tissue in normal and cirrhotic livers by chemical means Normal livers showed an average content of fibrous tissue of 1 9% of the dry weight of the liver with a range of 0 8 to 2 8% Cirrhotic livers had a fibrous tissue content of between 3 5% and 3% Thus it can be seen that some *microscopically cirrhotic livers have a fibrous* tissue content only slightly above normal The correlation between the microscopic and chemical estimation of fibrous tissue content was good in the lower concentrations but poor in the higher concentrations of fibrous tissue Thus the livers that showed 13 and 23% fibrous tissue were difficult to distinguish microscopically As would be expected there was an inverse ratio between the fibrous tissue content and the weight of the organ the smallest livers having the greatest amount of fibrous tissue

Fatty metamorphosis This change is one of the characteristics of portal cirrhosis The fatty livers are larger in size The fatty changes are likely to vary inversely with the fibrosis *As the fat disappears fibrous tissue increases* It is tempting to attribute a cause and effect relationship between these two processes but this has not been satisfactorily demonstrated In general the fat content in a truly cirrhotic liver does not reach the 40% level of non cirrhotic fatty livers A markedly fatty liver analyzed by Warren and Wahli showed only 2% fibrous tissue The lipoid material may distend the entire cell with a large fat droplet and push the nucleus to one side or the droplets may be minute and form small vacuoles in the cell cytoplasm If the fat content is not very great it requires specific stains for its demonstration since glycogen may also appear as vacuoles in the parenchymal cells

3 *Degeneration and necrosis* This development is variable in extent and depends on the activity of the disease This is one of the pathologic features that can be used in measuring the activity or latency of the process Cloudy swelling of the hepatic cells is frequently observed Mallory emphasized the presence of hyaline bodies in the hepatic cells and thought them to be characteristic of alcoholic cirrhosis but they have since been demonstrated in cirrhosis without a history of alcoholism The hyaline changes are simply a sign of degeneration and do not have the specificity formerly attributed to them Another change which may be indicative of degeneration has been noted by Post and co workers They demonstrated by histochemical studies



Fig 71 Early portal cirrhosis Needle biopsy of liver (× 70) showing mild fatty change periportal fibrosis polymorphonuclear cell infiltration bile duct multiplication

Patient is a 46-year old female with amenorrhea of 3 months duration Hepatomegaly lower edge 10 cm below costal margin Serum bilirubin 0 6 mg% Total protein 7 7 gm Albumin 3 3 gms Globulin 4 4 gms% Total cholesterol 141 5 mg% Esters 74% of total Thymol turbidity 4 6 units Flocculation 0 Cephalin cholesterol flocculation 2 plus BSP 16% retention

a golden brown granular deposit having basophilic properties in 90% of normal livers studied This pigment did not have the reactions of ceroid and was either absent or reduced in fatty livers and cirrhosis

Many cells may show loss of nuclei and disturbance of cell membrane indicative of necrosis The extent of this depends on the virulence and progression of the cirrhotic process In any event the necrosis is not the widespread rapid devastating process seen in acute hepatitis or other forms of acute necrosis The exact relationship between necrosis and fibrosis is still unsettled It seems however that fibrosis and nodular hyperplasia are reparative processes while necrosis and degeneration are the destructive processes In massive necrosis of any form neither regeneration nor fibrosis takes place

4 *Regeneration* The liver has a tremendous capacity for this and it is undoubtedly one of the means by which the organ tries to preserve its function The phenomenon of liver cell regeneration was described over 100 years ago by Cruveilhier (1833) The functional integrity of the newly formed parenchymal nodules may be doubted first because their relation ship to sinusoids and bile ducts are abnormal and secondly because the cells are morphologically different This suspicion of the physiological incompetence of the newly formed cells is heightened by the fact that patients may die from what seems to be liver failure in spite of numerous areas of regeneration sufficient to make up 20% of the liver volume which should be enough to carry on the vital functions The aspersions cast on regenerating parenchyma are directed only against the disorderly nodular regeneration of cirrhosis and not to the orderly regeneration within the bounds of the normal reticular structures

Regeneration can conceivably occur through mitosis and amitosis but the majority of observations indicate that the amitotic multiplication of cells predominates especially in the nodular regeneration The pre existing liver cells are the source of the newly formed liver cells This is supported by the early observations of Milne (1908) as well as the more recent ones of Ashworth and Reid (1947) Ashworth and Reid found evidence of intralobular regeneration in 63 out of 100 autopsies on patients who had neither primary liver disease nor cirrhosis Regenerating newly formed liver cells differ from mature liver cells by their larger and variable size clearer and more eosinophilic cytoplasm the larger nuclei with increased chromatin more prominent nucleoli multiple nuclei and syncytium containing many nuclei without cell boundaries Since these morphological characteristics of regeneration are found in both the nodular and intralobular forms of regeneration the morphological differences between the newly formed and mature liver cells cannot therefore be accepted as evidence of functional deficiency however function may depend on subtler changes than can be detected by the microscope It is therefore still possible that the cells in nodular regeneration are not as efficient as the intra lobular regenerating cells

5 *Bile duct multiplication* This is another feature of portal as well as other cirrhoses Aggregations of large numbers of small bile ducts are seen stranded in masses of fibrous tissue with an occasional single liver cell here and there The question may be properly asked whether this represents a concentration of pre existing bile ducts because of loss of parenchymal cells and the drawing together of several portal spaces by the contracting connective tissue or truly new formation of bile ducts Moon studied this problem by counting the number of bile ducts in a measured segment of liver in a normal and large cirrhotic liver and concluded that the cirrhotic liver contains fourteen times as many bile ducts as the normal organ

Mitosis of bile duct epithelium with elongation and tortuosity of the ducts has been noted in experimental obstruction of the common duct (MacMahon and associates) in animals While this cannot be directly applied to man and is another form of cirrhosis there is nevertheless no doubt that multiplication of bile ducts takes place in man It is not clear whether the multiplication is accompanied by tortuosity branching of the ducts or both

A question of greater importance which is also unsettled is in regard to the transformation of the bile duct epithelium into parenchymal cells Pearce (1906) after a study of

experimental liver injury in the dog concluded that such transformation does occur This transformation is doubted by others (Hershheimer and Thollote 1930 Karsner 1943) Lucke in his excellent pathological study of infectious hepatitis demonstrated that longitudinal sections of ducts lined by the typical cuboidal bile duct epithelium end in an ampulla composed of cells resembling the polygonal cells of the liver This author concluded that while such transformation may occur it is not important in the restoration of functional liver parenchyma Regardless of the final resolution of the problem the regenerating nodules arise predominantly from liver cells rather than bile duct epithelium

6 *Inflammatory cell proliferation* This is another morphologic feature of portal cirrhosis which factor may be surprising since this type of cirrhosis is no longer considered an inflammatory but a degenerative process Moschcowitz emphasizes the development of the periportal inflammatory cell even during the early stage of fatty metamorphosis and considers that they give rise to the newly formed capillaries and fibrous tissue In general the leukocytic reaction is not as marked in portal cirrhosis a cirrhosis following a truly inflammatory process such as hepatitis These cells are composed of both monocytes and polymorphonuclear leukocytes which are scattered in the fibrous tissue stroma

Portal cirrhosis has been divided into *latent* and *active* forms on the basis of several morphological features Signs of activity include

1 inflammatory cell proliferation
parenchymal necrosis and degeneration and
3 active proliferation of fibrous tissue

When none of these three features is present the cirrhosis is considered as inactive latent or healed These terms must be transferred with caution to the clinical picture for in pathologically inactive or healed cirrhosis there may develop a massive hemorrhage from esophageal varices or a sudden flare up of the disease with rapid progression The clinical indication of latency will be discussed later

7 *Variable changes in the liver* In patients with portal cirrhosis bile staining of hepatic cells may be present the degree of which depend on the degree of jaundice and the severity of bile stasis Some bile plugs may also be seen in the bile canaliculi These changes are usually mild in portal cirrhosis as compared with biliary cirrhosis and form a basis for differentiating the two conditions Deposition of a brownish nonbiliary pigment may also be detected This pigment resembles hemosiderin and is present in very small amounts except in hemochromatosis

Morphologic Differentiation

The pathological differentiation between true portal dietary cirrhosis and post hepatitic cirrhosis is a subject of frequent debate and discussion From a practical clinical point of view this differentiation is not too important since it is the functional capacity of the liver rather than its structural alterations that is of the utmost importance although there is some difference in prognosis of the two entities Again it is difficult to talk about differentiation until it is decided whether we are dealing with different entities Since it is maintained by some that an anatomical picture of portal cirrhosis may result from hepatitis (Howard and Watson Sherlock) these two etiologically different cirrhoses cannot be differentiated on anatomical grounds (Kelsall and co workers) Karsner also concedes that in the advanced stage the architecture may be so completely altered that the etiologic fingerprints are obliterated

The differentiation between post hepatitic and dietary cirrhosis can be made on morphological grounds when the former shows some of the features of postnecrotic cirrhosis The differential features of these two cirrhoses were well summarized by Baggenstoss and Stauffer They also point out that these differential features do not pertain to the finely granular type of post hepatitic cirrhosis for this is the type that resembles most closely the typical portal cirrhosis The main distinguishing features are the large regenerating nodules the broad strands of fibrous tissue and predominantly monocytic infiltration in the post hepatitic cirrhosis as opposed to the fine regenerating nodules (less than 0 5 mm and uniform in size) fine strands of fibrous tissue polymorphonuclear leukocytic infiltration and

fatty metamorphosis in dietary cirrhosis (Table 57 p 367)

Extrahepatic microscopic changes The spleen shows signs of congestion and fibrosis The congestion is evidenced by the dilated venous channels and periarterial hemorrhages However there is also a marked hyperplasia of the pulp Although this could be conceivably due to passive congestion the experiments of Cameron and De Saran indicate the possibility of other factors These workers dissociated the spleen from the portal circulation by marsupialization and produced cirrhosis with carbon tetrachloride The splenic pulp showed hyperplasia of its elements This suggests that the etiologic agent that produce liver injury may attack the spleen directly The pancreas may also show fibrosis This organ like the spleen may be influenced by the increased portal vein pressure Kirshbaum and Shure noted well developed fibrosis of the pancreas in 36 2% of their cirrhotics They also found cirrhosis in 50% of their patients with pancreaticolithiasis (see Chapter 44 for the relation of pancreas to liver)

The kidneys likewise may show changes of varying degree and character In patients with marked icterus the so called cholemic nephrosis may be demonstrated Other changes in the kidney are alluded to in Chapter 65 Because of the endocrine disturbance in liver disease the pathologic changes in the sex organs are of interest Bennett and co workers found an increased incidence of atrophy of testicular germinal epithelium and thickening of the lamina propria of the seminiferous tubules They also noted slightly increased frequency of metaplasia of prostatic epithelium and hyperplasia of mammary glands of male patients Changes in the brain are also of interest in view of the frequency of central nervous system symptoms in patients dying from hepatic failure The changes in the brain are of a non specific nature and are discussed in Chapter 74

Microscopic Pathology—Summary

Histogenesis
- **Fatty metamorphosis fatty liver fatty cirrhosis**
  - **early stage of portal cirrhosis**
- **Leads to fibrosis by**
  - **round cell infiltration giving rise to fibrous tissue (Moschcowitz)**
  - **compression of cells and vascular channels resulting in pressure atrophy and ischemic necrosis ending in fibrosis**
- ***Site of origin of fibrous tissue***
  - **difficult to determine**
  - **in cardiac cirrhosis—centrolobular**
  - **postnecrotic cirrhosis at site of massive necrosis**
  - **portal cirrhosis**
    - **centrolobular (?) (from fatty changes) and spreads peripherally or**
    - **periportal—at site of exudative process**
    - **portacentral (Popper and co workers)**
- **Intrahepatic circulatory impairment due to**
  - **fibrous tissue**
  - **nodular regeneration with impingement on arterial and venous channels**
- **Intrahepatic shunt between**
  - **branches of portal vein and hepatic vein**
  - **branches of hepatic artery and portal vein**

Histopathology
1. **Fibrosis**
   - **widespread**
   - **distorts all liver lobules**
   - **bands of fibrous tissue usually fine**
   - **quantity of fibrous tissue**
     - **normal—0 8 to 2 8% of dry weight**
     - **portal cirrhosis—3 5% to 23%**
2. **Fatty metamorphosis**
   - **when marked liver is larger**
   - **inverse ratio between fat and fibrous tissue**
   - **lipid may exist in one large droplet or numerous small droplets**
3. **Degeneration and necrosis**
   - **cloudy swelling**
   - **hyaline bodies of Mallory**
   - **golden brown basophilic granular deposit (Post and co workers) absent in cirrhotic livers**

loss of nuclei
distortion of cell membrane
4 Regeneration
attempt at maintaining functional integrity
nodular regeneration has poor functional potential because of abnormal relationship to
blood supply
bile channels and
abnormal cellular structure (?)
mode of regeneration
chiefly amitotic
from pre existing liver cells
5 Bile duct multiplication
absolute increase of bile ducts
multiplication of bile duct epithelium which results in
tortuosity and/or
branching of bile ducts
bile duct epithelium may give rise to polygonal cells but this is unimportant in regeneration
6 Inflammatory cells
monocytes and
polymorphonuclear leukocytes are scattered in the fibrous tissue and stroma
proliferation of inflammatory cells is a sign of activity other signs are
parenchymal necrosis and degeneration
active fibrous tissue proliferation
7 Pigment deposition
bile pigment in hepatic cells degree depends on biliary stasis less marked than in biliary cirrhosis
brownish hemosiderin like pigment present in small amounts
Extrahepatic Microscopic Changes
Spleen
Congestion
dilated venous channels
periarterial hemorrhages
Hyperplasia of pulp
Fibrosis
Pancreas
Fibrosis
Congestion from portal hypertension
Kidneys
Cholemic nephrosis more likely in biliary cirrhosis
Sex organs
Atrophy of testicular germinal epithelium
Thickening of lamina propia of seminiferous tubules
Metaplasia of prostatic epithelium
Hyperplasia of mammary glands of male patients
Brain
Changes are nonspecific (Chapter 74)

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Clinical Features of Portal Cirrhosis

Symptoms (Table 58)

The clinical picture of portal cirrhosis is characterized by insidious chronicity and variability of symptomatology and severity In typical portal cirrhosis the full blown picture take many years to develop and there is a prolonged and variable period of time when the symptoms are vague and subclinical Therefore when the disease is first recognized the symptoms may appear to be of short duration while the disease process has gone on for many years This early period may be compared to the prodromal period of acute diseases in which mild atypical symptoms occur but the nature

impotence and premature ejaculation Sterility is common to both sexes

Pruritus in the hepatic jaundice of portal cirrhosis is uncommon but it does occur When it occurs the jaundice is usually severe and may signify the presence of intrahepatic biliary obstruction Pruritus has been reported in 3 3 to 21 6% of cases although the latter figure includes other skin manifestations

Central Nervous System Cardiorespiratory and Urinary

Many other symptoms may be mentioned which may or may not be related to the liver disease Eructations and pyrosis may be associated with the other gastrointestinal complaints Headaches dizziness and insomnia are such frequent nervous system symptoms in other diseases and in functional disturbances that it is difficult to be sure that they are in any way related to the hepatic disease however because of the well known development of severe central nervous system symptoms in advanced hepatic failure one may wonder whether these symptoms are related to cerebral damage or cerebral dysfunction Another possible explanation for central nervous system symptoms is the toxic effect of excessive alcoholic intake However neither of these two explanations is valid in the majority of cases since these symptoms may be present in patients with early cirrhosis and in those that have no history of alcoholism

Chronic anemia from blood loss from bleeding varices may also cause headache and dizziness Palpitation and dyspnea may also result from the chronic anemia Ascites when marked can produce dyspnea Cough and even palpitation may also be produced by this mechanism A variety of urinary symptoms including polyuria nocturia and dysuria may be complained of They may be dependent on renal disease unrelated to cirrhosis Nocturia may be evident in cirrhosis with edema and ascites as it is in cardiac failure

Hemorrhagic Symptoms

Various hemorrhagic phenomena produce a series of dramatic symptoms with grave consequences These occur with such frequency that they should not be considered as a complication but rather as an episode in the life cycle of the disease Esophageal hemorrhage from erosion of a varix is the commonest and most serious of these symptoms (The pathogenesis of this is discussed in Chapter 49) Because the bleeding is so high up in the gastrointestinal tract hematemesis is the commonest manifestation with melena occurring later However I have seen a patient die from exsanguinating hemorrhages from esophageal varices without hematemesis at any time This however is the exception to the rule and melena without hematemesis favors a diagnosis of bleeding lower in the gastrointestinal tract Slow oozing from esophageal varices may not infrequently result in melena alone Ratnoff and Patek record only nine patients or less than 3% who showed melena alone however Douglass and Snell found 16.4% of their patients with melena without hematemesis This is higher than their figure for hematemesis which is 16 2% The incidence of hematemesis in other reports varies between 15 3% and 27.4% The two most startling facts about hematemesis are that it may be the initial symptom and at the same time mark the final episode of the disease

The hematemesis from bleeding esophageal varices has certain characteristics which may help to differentiate it from other causes of upper gastrointestinal hemorrhage This differential diagnosis is of utmost importance because of the therapeutic urgency (p 353)

While upper gastrointestinal hemorrhage in cirrhosis is most frequently due to varices of the esophagus or fundus of the stomach the varices may be difficult to demonstrate even by x ray and endoscopic techniques It is conceivable that submucosal varicosities even in the duodenum may be responsible for hemorrhage However mechanisms other than these anatomical changes may be responsible Hemorrhages from other orifices—the nose mouth rectum vagina and urethra—may be seen in the advanced stages of cirrhosis on the basis of hypoproteinemia Thrombocytopenia consequent to the splenomegaly of cirrhosis may also be responsible for these hemorrhages as well as subcutaneous ecchymosis I have seen

generalized hemorrhagic phenomena in severe hepatic disease without adequate biochemical or hematologic explanation Hypofibrinogenemia is a manifestation of advanced liver disease and rarely plays a role in clinical hemorrhage I am convinced that some other obscure mechanism is at fault

There is evidence that increased capillary fragility occurs in liver disease this is independent of thrombocytopenia and hypoprothrombinemia but may be associated with them Whitesell and Snell studied this problem in 70 patients with acute and chronic liver disease including portal cirrhosis They determined the capillary fragility by the Rumpel Leede technique There was no correlation among the three factors that contribute to bleeding tendency although the capillary fragility appeared slightly more frequent in patients with a thrombocyte count of under 137 000 their minimal normal value Stefanini and Petrillo studied 30 patients with liver disease along the same line and also concluded that increased capillary fragility is responsible for the hemorrhagic tendency in these individuals who have a normal or only slightly depressed prothrombin level insufficient to produce a hemorrhagic diathesis Fifty per cent of their patients fell into the group with increased capillary fragility as the dominant cause of hemorrhage

The pathogenesis of the increased capillary fragility is obscure Since there is no evidence of specific vitamin deficiency such as ascorbic acid a specific toxic effect on the capillaries may well be postulated However a faulty utilization of one of the antihemorrhagic factors such as ascorbic acid citrin or even vitamin K with resultant damage of the capillary wall is a distinct possibility

Spider angiomas constitute another possible cause of visceral or cutaneous hemorrhage Injury of one of these skin lesions can cause obvious hemorrhage Whether these trademarks of cirrhosis are situated in the gastrointestinal tract and therefore can give rise to hemorrhage is unproved This along with increased capillary fragility may be responsible for exsanguination in cirrhosis when no other source of bleeding can be detected at autopsy

In summary the various factors that may be responsible for hemorrhage in cirrhosis and any other form of liver disease are as follows

- I Vascular changes
  - A Venous collaterals
    - 1 Esophageal varices
    - 2 Hemorrhoids
  - B Increased capillary fragility
  - C Spider hemangioma
- II Chemical changes in blood
  - A Hypoprothrombinemia
  - B Hypofibrinogenemia
- III Changes in circulating formed elements
  - A Thrombocytopenia

Clinical Features—Summary

Functional Classifications
- **Decompensated**
  - **jaundice edema and ascites**
- **Compensated (latent)**
  - **productive of few symptoms**

Symptoms
- **Early dyspeptic symptoms**
  - **anorexia**
  - **nausea**
  - **bloating**
  - **eructations**
  - **vomiting (before breakfast in alcoholic group)**
- **Lower intestinal symptoms**
  - **diarrhea**
  - **constipation**
- **Abdominal distention**
- **Abdominal pain**
  - **Location**
    - **usually right hypochondrium**
    - **may be in epigastrium generalized or**
    - ***left hypochondrium***
  - **Character of pain**
    - **aching usually mild**
    - **cramping and severe (resembling biliary colic on occasion)**
    - **related to respiration occasionally**
- **Weakness**
- **Fatigue**

Endocrine symptoms
- **Female**
  - **dysmenorrhea**
  - **amenorrhea**

- painful breasts
- sterility

Male

- loss of libido
- impotence
- premature ejaculation
- sterility

Central nervous system symptoms

- Headache
- Dizziness
- Insomnia

Cardiorespiratory

- Palpitation
- Dyspnea
- Cough

Urinary

- Polyuria
- Nocturia
- Dysuria

Hemorrhagic symptoms

- Hematemesis, Melena — from bleeding esophageal varices
- Hemorrhage from nose, mouth, rectum, vagina, urethra — due to hypoprothrombinemia or increased capillary fragility

Physical Findings (Table 59)

Jaundice

Jaundice is both a symptom and a physical finding and it is well to use it as a starting point to enter into a discussion of the objective findings. The observation of the yellow discoloration of the skin or sclerae by the patient or more commonly by his friends may prompt the individual to seek medical attention. In my experience jaundice does not bring the patient with cirrhosis to the physician as in other types of liver disease. The reason for it is that jaundice is frequently absent in portal cirrhosis or when present may be so mild as to be overlooked by the patient.

Most statistics are obscure on the point as to whether the jaundice was reported by the patient as a symptom or found by the physician on examination. There is also a marked divergence between the reported incidence of jaundice and its intensity. I suspect that the reports showing a high incidence of jaundice of marked intensity include cases of biliary (cholangiolitic or post hepatitic) cirrhosis. The presence and intensity of jaundice is a useful clinical differential point between portal and biliary cirrhosis. Intense jaundice is a preterminal finding in portal cirrhosis while in biliary cirrhosis it may exist for years.

That jaundice is not a constant feature of *portal cirrhosis is emphasized by the report* of Spain. Of 250 autopsies in patients with portal cirrhosis clinically detectable icterus was present in 75 or 30%. The other 70% were either anicteric or had mild subclinical icterus. While many of these patients did not die as a direct result of the cirrhosis and 71%

TABLE 59

The Frequency of Physical Findings in Portal Cirrhosis

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Jaundice	65 3%	67%	51 %	33 1%	69 5%	9 5%	50%
Ascites	78 0	93	62 0	47 7	74 0	60 3	60 3
Fever	4 5	49	49 3		30 7		
Edema	61 1	69	59 1	34 9	40 8		
Dilated superficial veins	23 6	61	40 8	18 5	6 9		
Caput medusae	1 0+		10 0				
Hernias		33			7 6		
umbilical	4 4						
inguinal	3 6		7 0				
Palpable liver	75 4	79	70 0	70 9	71 1		
Palpable spleen	44 0	55	4 0	32 2	30 7		
Hemorrhoids	7		33 7		9 1		
Hydrothorax	6 5	17	10 0		8 6		
Spider angiomas	15 0	6		6 1			
Telangiectasias	17 0				45 1		
Palmar erythema	4 0+						

of thes were regarded as having had latent jaundice it is nevertheless true that this finding may be absent even in advanced portal cirrhosis and in individuals dying from it

The figures of Spain are lower than some found in clinical reports which varied between 33 1 and 69 5% (Table 59) The Chilean workers found jaundice as one of the initial complaints in 55 7% In this group the jaundice was mild in 20 6% moderate in 25 9% and severe in 23 0% Therefore 48 9% had moderately severe jaundice It is doubtful that the patients would themselves detect very mild jaundice

A preponderance of female patient may explain a report of an increased incidence and intensity of jaundice Spain pointed out that jaundice was twice as frequent and more inten e among h s female than among h s male patients The increased incidence of biliary irrhosis reported among females make one wonder whether this is again a question of erroneous classification but since Spain s series is an autopsy study this error is not likely to be of importance

While jaundice undoubtedly occurs as one of the presenting symptoms (Fagin and Thompson 1944 Armas Cruz and co workers 1951) it i much less common as an early symptom in po tal cirrhosis as compa ed with o her type of cirrhoses This is graphically illustrated by Baggenstoss and Stauffer In 43 cases each of post hepatitic and portal cirrhosis the presenting symptom of jaundice was seen 35 times in the former and only five times in the latter The presence or absence of pruritus is also helpful in this differentiation since as was pointed out before the jaundice of portal cirrhosis is usually unaccompanied by pruritus

Jaundice ha some prognostic value in portal cirrhosis in spite of the fact that advanced liver failure and death in this disease may be accompanied by icterus Jaundice may come and go but persistent progressive and severe jaundice is a poor omen Progressive jaundice is one of the signs of progressive liver necrosis The seriousness of jaundice was demonstrated by Ratnoff and Patek Of 168 fatal cases with jaundice death occurred in half of these within two months after the on et of jaundice and 85% of the patients died within one year

The seriousness of jaundice is unique in po cirrhosis since patients with other type liver damage may remain jaundiced for l periods of time This is further evidence t the jaundice in portal cirrhosis is chi hepatocellular in type

Fever

Fever is likewise an important finding f a prognostic and diagnostic point of v Although it occurs in one fourth to one t of patients with cirrhosis it is freque overlooked in discussions of this di ease S patients with cirrhosis are prone to infect of various types a complicating infec should be looked for Moreover the feve high may introduce marked diagnostic c fusion While the fever is usually low gr the empe ature may rise to 102 or 103 F with the diurnal variation suggests a pyog infection or specific systemic infection such typhoid fever or malaria The leukopenia splenomegaly further complicate the diagno problem I followed one patient for about months with a fever of this type with occa io chills leukopenia and splenomegaly T patient had resided in a tropical area wh malaria was endemic Several observers w convinced this patient had malaria but sm of the blood were always negative and history as well as the other clinical and labo tory findings favored cirrhosis At autop typical portal cirrhosis (Fig 68) was fou but no complicating disease to account for fever The fever is due to necrosis of liver c and absorption of their proteins It is theref a sign of progression and forebodes a f outcome

Ascites

Ascite is another finding in severe cirrho The term decompensated has frequently b applied to patients with ascites Ascites al with jaundice and fever indicates act progressive di ease and therefore a p prognosis However the outlook for a pat with ascites is not as gloomy as it was ye ago Although it is a sign of advanced dise the patient may consult the physician beca of a cites or its concomitant discomfort Th the patient may seek attention beca se

abdominal enlargement abdominal discomfort or dyspnea all of these being caused by the intra abdominal accumulation of fluid This indicates how insidiously cirrhosis may develop since the patient feels no need for medical care until the disease is in an advanced stage *The incidence of ascites in portal cirrhosis is* high in one of every two or three of every four patients with cirrhosis 47 7% to 78% (see Table 59)

Ascites is obvious on inspection when there is much fluid but occasionally some errors may occur in differentiating it from tympanitis With a patient lying on his back ascites is indicated by a bulging at the flanks and the flatness of the anterior surface of the abdomen A cross section of the abdomen would be oval In tympanitis (meteorism) the flanks do not bulge but the anterior abdominal wall pro trudes in the recumbent position In massive ascites the umbilicus may protrude and other hernias may appear The detection of shifting dulness is of course a classical means of de tecting ascites The detection of a fluid wave by tapping one flank with a finger while hold ing the flat of the hand against the other flank can be accomplished if the ascites is not too massive and the fluid is not under pressure

Pathogenesis of ascites The pathogenesis of ascites is of considerable interest not only from an academic point of view but because the mechanism of its formation may lead to more effective therapy Although a good deal has been learned about its pathogenesis there are still some points that have not been entirely elucidated In the present state of our knowl edge it seems most likely that several mecha nisms influence ascites formation and in any given case more than one of these is operating These mechanisms may be listed as follows

1 Venous obstruction (portal hypertension)
2 Lymph changes in flow and constituents
3 Capillary and endothelial damage
4 Blood osmotic pressure decrease (hypo albuminemia)
5 *Water and sodium retention due to*
   a increased mineral corticoids
   b increased antidiuretic substance

There is ample clinical and experimental evidence that portal hypertension alone is not the cause of ascites An attempt to correlate esophageal varices with ascites in clinical cir rhosis would lead one to reject this hypothesis Esophageal varices are unquestionably due to portal hypertension yet esophageal varices are frequently present in the absence of ascites *and the reverse is also true* There is poor cor relation between the most important clinical sign of portal hypertension and ascites

In animal experiments it is virtually impos sible to produce ascites by constriction of the portal vein alone Volwiler and associates pro duced marked portal hypertension in dogs by placing cellophane bands around the main portal vein and inferior vena cava below the liver but ascites did not develop in any of these animals However ascites developed when a reduction in plasma proteins was produced by plasmapheresis On the other hand constric tion of the inferior vena cava above the liver regularly resulted in the development of as cites within two or three weeks Concomitant with the development of ascites in these ani mals there was a drop in plasma proteins but this appears to be secondary to loss of circu lating proteins into the ascitic fluid

These experimental observations support the clinical experience that obstruction of the venous circulation above (proximal) to the liver as in hepatic vein thrombosis results in prompt development of ascites while acute obstruction of the portal vein may not always be followed by ascites In yet another respect the observations at the bedside confirm the observations in the laboratory I have re peatedly seen patients with various types of cirrhosis without ascites in whom ascites developed promptly after a massive hemor rhage from esophageal varices The hemorrhage acts as a plasmapheresis by lowering the plasma proteins Injection experiments in human cirrhosis with ascites seem to indicate that there is a diminution of intrahepatic tributaries of the hepatic vein and therefore in essence a hepatic vein rather than a portal vein obstruction is produced (Chapter 49)

The changes in lymphatic flow in ascites have been studied by Bollman and his associates at the Mayo Clinic They noted that constriction of the vena cava above the liver resulted in

marked hepatic congestion and enlargement of hepatic lymphatics. Nix and his associates studied the lymph flow and protein content of the lymph in dogs with constriction of the vena cava above the liver and in rats with cirrhosis produced with carbon tetrachloride. They found the lymph flow and the protein content of the lymph markedly augmented in both of these experiments. They suggested that increased permeability of the liver capillaries may result in these changes in the lymph. It is possible that changes in capillary endothelium may extend also to the serosal cells of the peritoneum and result in pouring out of fluid by this membrane and a loss of its ability to absorb.

The role of the plasma proteins in the development of ascites has been alluded to briefly above. The tendency to hypoalbuminemia results in a drop of intravascular osmotic pressure which could result in a leakage of protein-free fluid into the interstitial spaces and peritoneal cavity. In man, as well as in animals, when ascites develops acutely after blood (protein) loss, the ascites can be abolished by blood replacement. The relationship between the plasma proteins and ascites and edema in cirrhosis was noticed by Myers and Keefer in 1935. More recently, Bjorneboe and associates (1949) found a definite correlation between plasma osmotic pressure, which is a function of the proteins, and formation of ascites. These workers found that when the plasma osmotic pressure falls below a critical level of 220 to 240 mm. of water pressure, edema and ascites were almost sure to occur. They offered the following formula for calculating the osmotic pressure from the serum albumin:

$3.56A + G = K$

A = albumin in grams
G = globulin in grams
K = colloidal osmotic pressure, and is equal to 16 normally

If K is less than 14.2, the osmotic pressure is below the critical level and ascites and edema should be present. This formula was erroneous only once in their series of cases. The plasma protein determinations were done by the ammonium sulfate precipitation method.

Higgins and associates also found that there is a good correlation between plasma osmotic pressure and ascites formation. They stated that ascites is unusual unless the colloidal osmotic pressure is below 300 mm. of water or the serum albumin is below 2.5 gm. per 100 cc. They used the following formula proposed by Wells, Youmans and Miller in calculating the plasma osmotic pressure:

$P = C(5.9A + 21.4)$, where

P = total osmotic pressure in mm. of water
C = total proteins in grams per 100 cc.
A = albumin in grams per 100 cc.

Kark and associates postulate another mechanism besides osmotic pressure changes for the production of ascites in hypoproteinemia. They suggested that the albumin has an intracellular as well as an extracellular function and, when albumin was present in sufficient quantities within the endothelial cells, it formed a barrier against transudation of water. When albumin is depleted, not only does the osmotic pressure fall, but the albumin-depleted cells become more permeable to water and salt.

While the correlation between the serum albumin and ascites formation is usually good, there are enough exceptions to warrant the opinion that ascites may be present in spite of adequate protein levels and that ascites may persist even with heroic administration of albumin. Ralli and associates noted no marked difference in the plasma proteins between cirrhotics with and those without ascites. The loss of ascites with therapy preceded the rise in serum albumin. The sequence of events must be determined before one can assume that there is a causal relationship between the drop in serum albumin and formation of ascites. In some instances, one can be sure that a drop in albumin precedes the ascites formation; this is evident in ascites after plasmapheresis in animals and massive hemorrhages in man. However, in ascites caused by constriction of the hepatic veins, the hypoproteinemia followed formation of ascites. The loss of circulating proteins was due to the loss of these proteins into the ascitic fluid. Mankin and Lowell noted a similar phenomenon in man. They

found that diffusion of plasma protein into ascitic fluid was an important factor in ascites formation and that an equilibrium was established between the plasma osmotic pressure and the ascitic osmotic pressure An increase of plasma colloidal osmotic pressure did not result in a decrease of ascites but rather a loss of protein from the plasma and a gain of protein in the ascitic fluid

The use of *albumin labeled with a radioactive* atom would seem to offer an ideal way of solving this problem of exchange of proteins between serum and ascitic fluid The results from some of these studies are conflicting Ivor and his associates used albumin tagged with I^{131} They found the serum albumin depressed in their patients with cirrhosis and lower in those with ascites But the loss of the tagged albumin from the circulation was the same in the control group and in the cirrhotics with and without ascites during the first 48 hours At 48 to 72 hours the rate of disappearance in the cirrhotics with ascites was slower than in the other groups There was a significant decrease of urinary excretion of inorganic iodine Determination of radioactive content of the ascitic fluid was not done in these studies It was concluded from these observations that in cirrhotics especially those with ascites there was decreased synthesis and decreased turnover of albumin which is an important factor responsible for ascites formation

Observations made in experimental ascites in Whipple's laboratory with the use of C^{14} labeled plasma proteins yielded different results *Injections of labeled albumin and* globulin into dogs with experimental ascites showed that both of the plasma constituents entered the ascitic fluid freely indicating a free interchange of proteins between the two components Albumin apparently crossed the peritoneal membrane three times as rapidly as globulin and reached an equilibrium with the circulating protein in a shorter period of time

The conclusion that is justified at this time is that while hypoalbuminemia with a drop in serum colloidal pressure is undoubtedly important in the pathogenesis of ascites its importance is variable and not constant In certain situations apparently the hypoalbuminemia follows rather than precedes ascites formation

Ascitic fluid is not a static reservoir but shows rapid interchange of its constituents with the circulating fluids The rapid interchange of water between the peritoneal cavity and the circulation has been demonstrated by means of tritium labeled water (Prentice *and co workers 1952) As much as 40 to 80%* of the total ascitic fluid enters and leaves the peritoneal cavity each hour This rapid exchange occurs in patients with ascitic fluid indicating that the serosa is capable of absorbing as well as secreting Increasing volume of ascitic fluid is an indication that the serosal secretory capacity has exceeded its absorptive capacity

The role of sodium and water retention in cirrhosis with ascites is discussed at length in Chapter 64 There seems to be no question that liver damage results in water and salt retention and this is particularly marked in patients with ascites Increase of salt intake results in increase of ascitic fluid (Eisenmenger 195 Goodyear 1950 Kark and associates 1951) The retention of sodium depends upon increased mineral adrenocorticoids and increased elaboration of an antidiuretic substance (Chapter 64) The interrelation of the various factors involved in ascites production is demonstrated by a recent study of Schilling and associates (1952) These workers found that occlusion of the vena cava above the liver a procedure that results in ascites also results in marked sodium *and water retention While occlusion of the* portal vein or vena cava below the liver does not result in electrolyte disturbances a decrease in serum albumin has also been demonstrated in this experimental procedure The various factors discussed above are undoubtedly interrelated in the production of ascites in human cirrhosis and should be kept in mind in the treatment of this serious sign of liver disease (Fig 7-)

Edema is an expected concomitant of ascites however it is a good deal less common This discrepancy between the frequency of ascites and edema emphasizes that there are some local factors operating in addition to osmotic

pressure and electrolyte changes If these physicochemical factors were the only ones responsible peripheral edema should be as common as ascites One may even surmise that the discrepancy may be greater than the statistics indicate since minimal edema should be more easily detected than minimal ascites However it must also be admitted that a good deal of extracellular fluid accumulation may occur before it can be detected as edema

Edema is noted in one third to two thirds of patients with cirrhosis (Table 59) and like ascites is a sign of advanced disease It is usually seen in association with ascites when the edema is most marked I have seen it on occasion in cirrhotics who showed no detectable ascites it is likely that in such cases the ascites is minimal and not detected by physical examination The edema is most commonly found in the lower extremities when the patient is ambulatory and in such cases is more marked in the evening and may disappear after a night s rest Scrotal edema and edema of the abdominal wall may also occur but usually this peripheral edema is not as marked as in congestive heart failure Marked anasarca favors other causes of edema (Case 11) this is especially true if marked edema is present without ascites Edema of the face in uncomplicated cirrhosis is very rare but it has been described (Pratt and Stengel)

Dilated superficial veins are frequently detected in cirrhosis with and without ascites but is commoner in the latter They are usually periumbilical running radially from the umbilicus like spokes of a wheel They represent collaterals connecting the umbilical or periumbilical veins with the internal mammary and deep hypergastric The blood flow in portal vein obstruction is radially away from the umbilicus in inferior vena cava obstruction the blood flow is entirely cephalad and in intrathoracic venous obstruction the blood flow is caudad Marked dilatation of the periumbilical veins with formation of caput medusae is rare in portal cirrhosis only about 1% showing

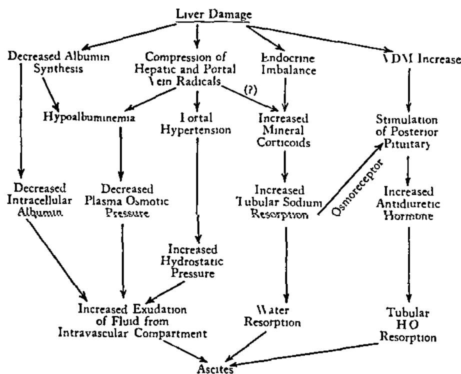


Fig 7 Schematic presentation of factors involved in the pathogenesis of ascites



Fig 73 Photograph of abdomen and thorax of patient with portal cirrhosis and marked ascites
A Photograph with ordinary light
B Photograph with infra red light Note the large and numerous venous channels seen with the infra red light Also noteworthy are the pectoral alopecia and umbilical hernia

such marked dilatation of the abdominal veins while less marked venous dilatation is detected *in 20 to 40% of patients*

The detection of these dilated abdominal venous channels is facilitated by infrared photography (Fig 73) A simpler and more direct way of detecting these increased venous channels is by inspection of the abdominal wall with red goggles While accommodating my eyes for fluoroscopic examination I was frequently startled by the visible venous channels *which could not be seen with the naked* eye This observation has been reported by others (Ingegno and Merrill) These dilated superficial abdominal veins have been used for visualization of patent umbilical veins roentgenographically and for estimating portal pressure (p 352)

A *murmur* and *thrill* over the upper abdomen have been described in the Cruveilhier Baumgarten syndrome (Chapter 47) Audible murmurs or hums have been noted in patients who do not show a caput medusae or extensively dilated abdominal veins Bloom recently discussed the problem of venous hums in cirrhosis and reported two unusual cases One patient showed a venous hum which extended from the xiphoid upward and to the right being *audible over the major portion of the right* anterior chest Pegot in 1833 was the first to report a venous murmur in a patient with portal cirrhosis The adventitious sound is humming in character usually not related to cardiac systole or respiration although systolic and inspiratory accentuation has been reported The point of maximum intensity is the umbilicalor xiphoid region and is due to an abrupt *change in the size or direction of two anastomotic* veins

Hernias become apparent during examination of the abdomen in a small percentage of patients with cirrhosis This is especially true in patients with ascites The markedly increased intra abdominal pressure is responsible for the production of hernias through the weak areas in the abdominal wall Apparently because of the peculiar direction of the intra abdominal pressure umbilical hernias are commoner than inguinal hernias The umbilicus may protrude markedly and show a bluish discoloration because of a dilated venous plexus in that region (Fig 73) The hernias may disappear

after the disappearance of ascites if they are small and entirely due to the increased intra abdominal pressure

The *liver* is palpable in about 70% of patients It is preferable to use the term palpable rather than hepatomegaly since the deductions about the size of the liver from clinical examination are not always accurate Most writers on the subject use the two terms interchangeably but this is erroneous A palpable liver can be smaller than normal normal or enlarged One must detect the level of the upper margin of the liver in order to estimate more accurately its size The normal liver is frequently palpable 1 or 2 fingerbreadths below the costal margin on deep inspiration therefore the term hepatomegaly ought not be used clinically unless the liver is 5 cm or more below the costal margin and the upper border is in the fifth interspace in the midclavicular line When the anteroposterior diameter of the liver is increased as evident by bulging of the liver against the anterior abdominal wall hepatomegaly is likely to be present This type of liver not only can be palpated easily but can be detected on inspection as well It is obvious from correlation with autopsy data that hepatomegaly is not present in 70% of cases with atrophic cirrhosis At autopsy about half of the livers are below normal in weight and many of the slightly enlarged livers are not sufficiently enlarged to be detected clinically so that this high incidence of palpable livers is deceptive about actual liver size I am certain from follow up of some of these patients to autopsy that some small livers are palpable and considered enlarged clinically Ratnoff and Patek reported that in a group of palpable livers the weight range was 695 to 5100 gm while in a group of nonpalpable livers the weight range was 570 to 2900 gm

There is however one possible explanation for a higher incidence of hypertrophic livers from clinical observation and that is by the time the liver reaches the pathologist it may have shrunken from the loss of fat and the contraction of fibrous tissue The loss of blood during its removal will also decrease its weight The consistency of the liver is also important The liver may be soft firm or hard smooth granular or irregular A smooth soft or moderately firm enlarged liver is probably fatty the so called fatty or hypertrophic stage of portal cirrhosis As the fat decreases and the fibrosis increases the liver becomes firmer and even hard and the surface may feel irregular or granular Gross nodularity is not palpable in uncomplicated portal cirrhosis because the nodules are not sufficiently enlarged to be palpable through the skin and subcutaneous tissue

Tenderness is uncommon in cirrhosis when present it is mild Tenderness is never present in the latent phase of cirrhosis but may be elicited when there are signs of progressive hepatocellular necrosis Tenderness is therefore seen along with progressive jaundice and fever and is a poor prognostic sign It may also signify superimposed hepatitis

Palpability of the *spleen* is a more important clinical finding than palpability of the liver However before the spleen becomes palpable it becomes enlarged to at least twice the normal size hence low grade splenic enlargement is not easily detected clinically Special care must be exercised in palpating for splenic enlargement and because of its clinical significance it is well worth the clinician s time and effort

There are several methods of palpating the spleen and they should all be utilized before one decides that the spleen is not palpable Relaxation of the abdominal muscles by flexion of the legs is helpful in any abdominal palpation and should be utilized in palpating for the liver as well as the spleen The spleen can be palpated with the patient lying on his back arms at his sides and the examiner standing on the right side of the patient The examiner s left hand is placed posteriorly in the left lumbar region and with gentle pressure the structures are brought anteriorly and medially at the same time the right hand placed flat in the left hypochrondrium palpate for the spleen while the patient inhales I prefer palpating for the spleen by standing on the left side of the patient while holding the left lumbar area with the left hand I hook the fingers of the right hand over the left hypochondrium Occasionally a barely palpable spleen can be felt this way because of the

higher tactile sensitivity of the balls of the fingers which are used in this maneuver The third method utilizes gravity to bring the spleen to the midline the patient lies on the right side with the elbow or a pillow between the iliac crest and the lower edge of the chest cage The spleen can again be palpated by the flat of the hand or by the fingers hooked under the left costal margin

If the patient and the examiner are relaxed and unhurried a spleen of 300 gm or more should be detected by one of the maneuvers described An enlarged spleen can be missed for one of several reasons A markedly enlarged spleen may be missed because it is looked for high under the costal arch while it extends several fingerbreadths down The spleen normally enlarges down and medially occasionally it seems to descend directly down in the lumbar gutter like a kidney and be thus missed Ascites interferes with hepatic and splenic palpation and occasionally when ascites is massive accurate palpation must await paracentesis However if the liver and spleen are sufficiently enlarged they can be palpated by ballottement because they float in the ascitic fluid

Percussion of splenic dulness may give some idea of the size of the spleen but this is not as accurate as palpation When palpation is difficult because the patient is unable to relax dulness on percussion below the left costal margin on deep inspiration indicates descent of the spleen to that point and splenic enlargement Roentgen visualization of the spleen will be discussed later (page 4 0)

The size of the spleen varies a good deal clinically as well as pathologically This organ may be barely palpable or markedly enlarged dwarfing the hepatic enlargement Marked enlargement indicates portal hypertension one must therefore look for collaterals in the esophagus and elsewhere as well as the hematological changes of hypersplenism

Abdominal masses caused by edematous appendices epiploicae were described by Rosenak and Young These were freely movable nontender and situated in the epigastrium and left lower abdominal quadrant

Hemorrhoids like esophageal varices and dilated abdominal veins are sequelae of portal hypertension Because of their frequency in the general population their presence cannot be unqualifiedly attributed to portal hypertension Their occurrence in 9 1 % of the Armas Cruz series is hardly higher than in the general population They are seen in about one third of the patients in other series but unless they are very large and troublesome they should not be attributed to the cirrhosis They are commoner in patients with ascites and this pressure of the ascitic fluid may be a factor in their formation When the hemorrhoids are large and bleeding their relationship to the increased portal pressure is more probable *However these varicosities unlike those in* the esophagus never bleed profusely and if they did control of the hemorrhage would not present a great problem Slow oozing from hemorrhoids may contribute to the anemia of cirrhosis

Hydrothorax is related to ascites and does not occur in its absence except perhaps extremely rarely It is not a common finding since one out of five to 1- patients with ascites develop hydrothorax However Higgins and associates found hydrothorax in 10 out of 13 patients with ascites who came to autopsy but in one of these carcinomatosis was a complicating feature Some of these effusions are mild so that they are detected either on x ray or post mortem while others are massive yielding several liters of fluid (McKay and coworkers) Either or both pleural cavities may be involved at a given time As in pleural effusion of cardiac origin it is most commonly found on the right side Bilateral distribution of fluid is next in frequency and the least common is left sided involvement alone

The source of the pleural fluid has been a matter of discussion Because of its association with ascites it was thought that it may enter the pleural cavity by leakage through the diaphragm this would be more likely to occur on the left side even so it would *have to go* through the diaphragm and the parietal pleura before entering the pleural cavity However right sided pleural effusion has been demonstrated to be due to direct communication between the pleural and peritoneal cavities by

the rapid passage of dye and air from one cavity to the other and by the decrease of ascites after thoracentesis One such case which seemed to result in a peritoneopleural fistula owing to rupture of the diaphragm from a severe cough was recently reported by Williams

The more likely pathogenesis of hydrothorax is through the same defects involved in ascites formation with the exception of portal obstruction which plays no role in hydrothorax Hypoproteinemia and water and salt retention may produce hydrothorax as well as ascites In all the cases of hydrothorax reported by Higgins and associates there was a low plasma osmotic pressure Another possible cause for hydrothorax is an inflammatory process below the diaphragm such as perihepatitis and peripleuritis

The pleural fluid is usually low in specific gravity clear amber and low in protein content resembling a transudate However occasionally the protein content is high In itself this would suggest an exudate but since ascitic fluid may be high in protein content and the pleural fluid may originate from the peritoneal cavity its high protein content may depend on the protein content of the ascitic fluid Occasionally the fluid is bloody instead of straw colored The bleeding may be related to the bleeding tendency of cirrhosis as discussed above

Other causes of hydrothorax must be considered especially when the fluid is bloody Coexistent congestive heart failure may be present but tuberculosis which is not an infrequent complication of cirrhosis must also be ruled out A bronchiogenic carcinoma or a metastatic carcinoma must also be excluded before the hydrothorax is accepted as part of the cirrhosis

Cardiorespiratory findings include cyanosis which is most likely to occur in the presence of massive ascites which interferes with respiration There has been some suggestion that subnormal arterial oxygen saturation exists which may be dependent on some faulty enzymatic process (Keys and Snell) Dyspnea is also seen in ascites and this would be further accentuated by hydrothorax Tachycardia is also observed anemia would contribute to the development of this sign as well as dyspnea *Extrasystoles have also been observed* but may not be related to the hepatic changes per se The possible effect of liver disease on the heart is discussed in Chapter 66 Hypotension is frequently observed in cirrhosis while hypertension is rare Armas Cruz and coworkers observed hypotension in 10 of their cases The pathogenesis of hypotension is discussed in Chapter 65 Hydropericardium is a very rare complication and only a few cases have been described in the literature Barrera found 11 patients among 157 cirrhotics with hydropericardium but his experience is unusual Most refer to single cases (Talley Laurie) Because of its rarity this finding should make one look for other possible causes for its formation

Lesions of the Skin and Its Appendages

The skin demonstrates many abnormalities in cirrhosis Scaling exfoliation and infections of various types are associated with vitamin deficiency and are discussed in the appropriate section (page 4 4) In jaundiced individuals the skin is discolored by deposition of bilirubin The skin in patients with long standing liver disease develops a brownish pigmentation owing to melanin This pigmentation is especially marked in the exposed surfaces but is also present elsewhere The melanosis is more marked in individuals who have been jaundiced for a long period of time but its intensity does not bear a direct relationship to the hyperbilirubinemia The melanosis persists after the disappearance of jaundice

Spider Angiomas

The peculiar vascular formation variously known as spider angioma spider nevus spider telangiectasis nevus araneus cutaneous arterial spider or stellar nevus is one of the diagnostic findings of cirrhosis although it is not always present in cirrhosis and is occasionally seen in noncirrhotic individuals The first reference to vascular spiders is credited to an English dermatologist Erasmus Wilson in 1869

Frequency While spider angiomas are most frequently seen in chronic liver disease they are also seen in acute and subacute liver in

jury that has lasted for several weeks The exact incidence in cirrhosis varies a great deal with the nature of the report Thus reports of large series of cases that consist of analysis of case histories recorded by numerous observers does not give as high an incidence as reports of cases observed specifically for this lesion Thus the incidence of spider angiomas in the large series of Ratnoff and Patek was 15% and in the 444 cases analyzed by Douglass and Snell the incidence was 26 1% while in the classical studies by Patek and associates in 1940 48 out of 63 patients with cirrhosis exhibited this lesion In Bean s thorough survey 74 out of 101 patients with portal cirrhosis showed the presence of spider angiomas The greater frequency recorded by these observers is the true incidence while the scarcity reported in the other series of cases is erroneous owing to omission by observers who did not search for this lesion Post mortem studies do not contribute to the analysis of its incidence since the angiomas fade or disappear after death

There seems to be a racial difference in their development They are rare in Negro males and have not been observed in Negro women (Bean)

Spider nevi are seen less frequently in other forms of liver disease They occur in biliary cirrhosis hemochromatosis and infectious hepatitis In the latter it is likely to occur in the more prolonged cases or the ones that progress to chronic hepatitis or post hepatitic cirrhosis They are very rare in acute hepatitis with rapid convalescence Occasionally they develop in subacute toxic hepatitis but very rarely in post hepatic jaundice (see Table 60)

It has been observed in patients with non hepatic diseases, foremost among which are alcoholics and malnourished individuals Since these conditions may be precursors of cirrhosis it may be suggested that the vascular lesions herald the development of cirrhosis Spider nevi may be seen in various types of vitamin deficiency Pregnancy may be accompanied by the development of vascular spiders undistin-

TABLE 60

The Occurrence of Vascular Spiders in Persons with Hepatic Disease

Type of Disease	White Males		White Females		Negro Males		Totals	
	With Spiders	Without Spiders	With Spiders	Without Spiders	With Spiders	Without Spiders	With Spiders	Without Spiders
Laennec s cirrhosis	61	19	1	3	1	5	74	7
Cirrhosis and hepatoma	3	1	1	0	0	0	9	1
Cardiac cirrhosis	4	7	0	5	0	2	4	14
Fatty liver	1	1	0	1	0	0	1	
Hemochromatosis	1		0	0	0	0	1	2
Hepatitis (catarrhal jaundice)	5	5	3	7	0	2	8	14
Post arsphenamine hepatitis	1	1	0	0	1	1	2	[illegible]
Weil s disease	1	3				4	1	7
Post bismuth hepatitis			1				1	
C mma of liver			1		1			
Chronic alcoholism and lobar pneumonia		18		5		11	2	34
Common duct stone with jaundice		4		5		4	2	13
Carcinoma of head of the pancreas		3		1		2		6
Carcinoma of rectum with hepatic metastasis		3	1	3			1	6
F lty syndrome	1						1	
Total	8	67	19	[illegible]0	[illegible]	31	104	128

No spiders were encountered in female Negroes

From Bean Medicine 4 243 1945

guishable from those seen in cirrhosis The pregnancy may be and usually is perfectly normal unaccompanied by toxemia or evidence of hepatic injury They usually appear between the second and fifth months and disappear after parturition They may recur during succeeding pregnancies Bean in his masterly review mentions the following diseases in which cutaneous spiders have been noticed xeroderma pigmentosum scleroderma rheumatic fever Cushing s syndrome and thyrotoxicosis Since in some of these conditions hepatic injury i known to occur their dependence on occult liver disease cannot be excluded They have been demonstrated in normal individuals in whom liver disease could not be suspected or implied These lesions are usually smaller not fully developed and less numerous than in individuals without hepatic disease

Pathogenesis The development of these lesions in patients with liver disease and pregnancy directed attention toward endocrine imbalance In pregnancy they are likely to appear when the estrogenic stimulus is strongest and disappear after gestation The relationship to hyperestrogenism is an attractive theory but not conclusively proved by the hormonal studies of patients with liver disease (Chapter 63) although Bean (194-) strengthened this hypothesis by producing vascular spiders in two out of three alcoholics by oral administration of diethylstilbestrol It has also been theorized that increased intra abdominal pressure such as occurs in pregnancy and cirrhosis with ascites is a responsible factor This theory is even weaker for these lesions are observed in the absence of ascites and therefore in the presence of a normal intra abdominal pressure In my experience those with ascites are likely to show larger and more numerous lesions however Bean found ascites just as frequent in his group with and without spider angiomas

The nature of this vascular lesion was studied carefully by Patek and associates their observations are just as valid today as they were ten years ago They found that this acquired angioma differs from the congenital lesion *The direction of blood flow is from the center to the periphery* This can be demonstrated to one s satisfaction by compressing the central elevation with a pencil and noting the blanching of the entire lesion In the larger lesions pulsation can be detected which suggests its arterial nature The arterial nature of the vessels involved has also been demonstrated by its lack of obliteration when the extremity is elevated above the level of the heart and by its continued pulsation after a blood pressure cuff has been inflated above the venous pressure The pressure in these arterioles is below the systolic arterial pressure probably because of the small size of the vessel Patek and his associates described two lesions histologically One is essentially a central arteriole with branches radiating from it the other resembles more the arterial side of an arteriovenous aneurysm

Their distribution is confined almost exclusively to the upper portion of the body It has been stated that they never involve areas drained by the inferior vena cava This is not quite true I have seen them in the lower extremities and this is also reported by Bean They are most commonly found on the upper thorax neck and upper extremities They are concentrated especially over the manubrium sterni and in the region of the clavicles The shoulders and upper arms are also frequent locations while they are rare on the hands and fingers (Fig 74) and extremely rare on the lower extremities When they are widely distributed they are usually numerous and large This was the case in one patient that I saw who had them on the lower extremities abdomen and both upper extremities including the hands and fingers Some of these lesions were *over 2 cm in diameter* and from a distance the patient looked like he was covered with a curious rash Occasionally the distribution is atypical as in one patient who had none over the upper sternum a few on the back of the neck but the largest one in the right cubital fossa several on the hand and one well developed one on a finger

They may also be seen in the nasal oral and pharyngeal mucous membranes Their presence lower in the gastrointestinal tract is *conjectural* since they cannot be identified after death The lesions vary in number from



Fig 74 Shows spider nevi of hand and fingers in a patient with portal cirrhosis Note the raised central *arteriole and radiating vessels from it This is an unusual location for this lesion*

one or two to dozens The greatest number seen in a single subject by Bean was 124

The significance of these vascular lesions is chiefly diagnostic but they may give rise to profuse hemorrhage when traumatized Their arterial structure is responsible for the briskness *of the hemorrhage while their exposed position* makes them highly susceptible to injury When the bleeding spider nevus is situated in the mouth or pharynx it may give rise to a puzzling diagnostic situation It is possible that occasionally these lesions may be responsible for unexplained hemorrhage in cirrhosis in the absence of esophageal varices

Telangiectasias

Cutaneous telangiectasias not of the typical spider variety are also frequently found in cirrhosis of the liver They are probably more *frequent than the typical spider nevi but their* diagnostic significance is diminished by their frequency in noncirrhotic individuals They are of course frequently seen in individuals who imbibe excessive amounts of alcoholic beverages The massive telangiectasia of the nose in acne rosacea is a conspicuous mark of a tippler In these individuals hepatic injury may be suspected Telangiectasias of the exposed areas *of the body face and neck of individuals exposed to the sun such as farmers* and sailors is extremely common and no valid connection with hepatic injury can be established in these The development of telangiectasias in alcoholics and those exposed to the sun may be related to the repeated cutaneous vascular dilatation *that these individuals are subjected to The concurrence of* telangiectasias and spider nevi suggests that they may both depend on the same stimulus and vascular dilatation may be such a stimulus Indeed it has been suggested that the spider nevus telangiectasias as well as the *palmar erythema to be discussed shortly may be mechanisms of disposing of excessive* amounts of heat

The distribution of telangiectasias about

the face, neck and shoulders is similar to the areas of predilection of spider nevi. The atypical telangiectasias may develop first and gradually the more typical and diagnostic lesions evolve. It is not uncommon to see a typical spider nevus in the midst of an area of disorganized telangiectasias. Telangiectasias are commoner among cirrhotics with an alcoholic history and commoner among males. Isolated spider nevi, as was mentioned, are more frequent even among normal nonpregnant women than among normal men.

Palmar Erythema

Another cutaneous manifestation not infrequently seen in cirrhosis is the so called palmar erythema or "liver palms." Its relationship to alcoholism and cirrhosis was expressed by the connotation "beer drinker hands" used by Weber *in 1901*. It consists of a mottled redness of the thenar and hypothenar eminences that stand out by contrast with the paler color of the rest of the skin of the palm. The redness frequently involves the balls of the fingers and the plantar surface of the foot. The latter is referred to as plantar erythema. Not infrequently it is seen in conjunction with telangiectasias and spider nevi and, therefore, similar pathogenetic relationships have been evolved. It has been suggested that palmar erythema may likewise be dependent on hyperestrogenism and that it serves as an apparatus for the increased loss of heat.

It is not nearly as peculiar to liver disease as the spider nevus, since it is seen in many chronic illnesses, especially those accompanied by loss of weight and cachexia. It is frequently noted in rheumatoid arthritis, chronic malnutrition and the cachexias of malignant neoplasm. An attempt has been made to correlate it with hypoproteinemia, since the conditions it occurs in are characterized by low plasma proteins (Johnson and Hecht).

Palmar erythema, while an interesting finding, is neither frequent nor diagnostic of liver disease. While my impression is that it is slightly commoner in liver disease than in other chronic disease, some statistics seem to contradict this. Thus, Ratnoff and Patek noted palmar erythema in slightly over 4% of their cases, while Johnson and Hecht found it in between 5 and 7.9% of a group of nonhepatic chronically ill patients.

Changes in Finger Nails

Various changes in these appendages of the skin have been noted by students of cirrhosis. Clubbed fingers and curved finger nails were found in 5.4% of Ratnoff and Patek's group of 386 patients and in 18% of patients of Patek's more recent smaller group. These changes are not due to concomitant pulmonary involvement, since none of these patients had independent pulmonary disease and only three of their [illegible] patients had cyanosis and five had dyspnea. Most of these patients with finger nail changes have long standing and advanced cirrhosis; many have ascites. It is not due to decreased oxygen saturation of the blood, but is a sign of the chronic malnutrition which is etiologically related to the cirrhosis. Recently (1951) flattening of the finger nails in various types of cirrhosis was described by Kleeberg. He observed this change in advanced cirrhosis with accompanying signs of malnutrition. The thumb may be the first digit to become involved, and the condition spreads to the index and middle fingers. The nail may be smooth or lined by parallel grooves.

Physical Findings Related to Endocrine Imbalance

The symptoms that point to endocrine imbalance, such as dysmenorrhea, amenorrhea and hypermenorrhea in the female and sexual disturbances in the male, have been alluded to on page 391. The physical findings indicative of hormonal disturbance are discussed in Chapter 63. The frequency of the findings that point to imbalance of the sex hormones is emphasized by the studies cited in that chapter. These signs include loss of body and axillary hair, pectoral alopecia, gynecomastia, testicular atrophy in the male and mammary changes in the female. Clinicians are becoming more conscious of these changes, and, therefore, their incidence in the recent reports has increased. Ratnoff and Patek in 1942 mentioned only scanty body hair in 6.5% of their patients and pointed out that none of their patients demon

strated gynecomastia In the series of cases reported by Armas Cruz and co workers evidence of endocrine disturbances were noted in 50% of the men and amenorrhea was present in 59% of the women

The possible relationship of spider nevi and palmar erythema to hyperestrogenism has been mentioned (p 405)

While pectoral alopecia is frequently seen in portal cirrhosis and is a helpful diagnostic point I am not convinced that it follows the endocrine derangement of the disease but rather is a constitutional feature of patients prone to develop the disease In the Cook County Hospital series pectoral alopecia was specifically mentioned by the pathologist in 76 of the 244 male patients an incidence of 31% This may even be higher for in only 89 patients was the hirsutism of the chest mentioned Axillary alopecia is a better index of hyperestrogenism than pectoral alopecia and is frequently found in association with testicular atrophy

Gynecomastia is not an infrequent finding in liver disease It may be unilateral or bilateral and is not a sign of advanced disease It may occur in mild cirrhosis and even develop when the patient is improving I have seen it in male patients recovering from viral hepatitis This so called refeeding gynecomastia was recently emphasized by Kark and his associates The pathogenesis of nutritional or refeeding gynecomastia is obscure A delayed recovery of the estrogen inactivating properties of the liver is a possibility while an increase exogenous intake of estrogens from the food along with a mild continued impairment of liver function has been mentioned as another possibility

Testicular atrophy is a common finding in active advanced cirrhosis The testicular atrophy can be demonstrated both histologically and clinically Rather found histologic testicular atrophy in 17 out of 20 patients with active portal cirrhosis and in only 5 out of 15 cases of inactive cirrhosis The atrophy is usually reversible with functional recovery of the organ when the liver disease improves Lloyd and Williams found testicular atrophy as determined by the size of the testes in 75% of patients with advanced cirrhosis A testis under 4 5 by 2 5 by 2 5 cm was considered atrophied In view of the fact that the correlation between weight and histologic evidence of atrophy is not always perfect a slight decrease in size of the testes is not reliable as an index of atrophy Testicular atrophy is rare in patients under 40 and the incidence increases with age

Physical Findings—Summary

Jaundice
- **Usually mild**
- **May be absent**
- **Intense in advanced disease only**
- ***No pruritus***
- **Persistent and progressive equals poor prognosis**

Fever
- **Occurs in 1/4 to 1/3 of patients**
- **Usually low may reach 102 or 103° F**
- **Sign of activity**
- **Indication—poor prognosis**

Ascites
- **Bulging at flanks**
- **Shifting dulness**
- **Fluid wave**
- **Hernias appear in massive ascites**

Edema
- ***In 1/3 to 2/3 of patients***
- **Usually lower extremities—worse at night**
- **Scrotal edema**

Dilated Superficial Veins
- **Most common with ascites**
- **Periumbilical—radiating from umbilicus They shunt the blood into**
  - **internal mammary**
  - **deep hypogastric**
- **Caput medusae in about 1%**
- **More readily detected by means of red goggles or infrared photography**

Murmur and Thrill
- **Noted in patients without caput medusae**
- ***Maximum intensity over***
  - **xiphoid or**
  - **umbilicus**

Hernias
- **Umbilical most common**
- **Inguinal also occur**

Palpable Liver
- 70% of patients
- Consistency
  - soft
  - firm
  - hard
  - smooth
  - granular
  - irregular
- Tenderness uncommon when it occurs it is a sign of activity

Palpable Spleen
- 24 to 55% of patients
- Splenic enlargement indicative of portal hypertension

Hemorrhoids
- Not as important as esophageal varices

Cardiorespiratory Findings

Hydrothorax
- Related to ascites
- 8 to 20% with ascites develop hydrothorax
- Right sided most common
- Bilateral next common
- Left sided least common
- Pathogenesis of Hydrothorax
  - Leakage of ascitic fluid through diaphragm
  - Hypoproteinemia and
  - Water and sodium retention
  - Inflammatory process below diaphragm
- Characteristics of Pleural Fluid
  - Low specific gravity
  - Clear amber
  - Low protein content occasionally this is high when originating from ascites
  - Occasionally bloody from hepatic bleeding tendency
- Other Causes of Hydrothorax to be *Excluded*
  - Congestive heart failure
  - Tuberculosis
  - Bronchogenic carcinoma
  - Metastatic carcinoma

Cyanosis
- Due to ascites mechanical respiratory interference
- Subnormal arterial oxygenation

Dyspnea
- Related to ascites

Tachycardia

Extrasystoles

Hypotension
- May be related to increased VDM

Hydropericardium
- Is a rare complication

Lesions of the Skin and Its Appendages
- Melanosis
  - Related to icterus
  - Most marked in exposed areas

Spider Angiomas
- Incidence varies between 15 and 73% the latter is the more accurate
  - Less frequent in other types of liver diseases
  - Occur in nonhepatic conditions
    - normal individuals
    - malnutrition
    - alcoholism
    - pregnancy
- Pathogenesis
  - Hyperestrogenism
  - Increased intra abdominal pressure
- Nature of Lesion
  - Central arteriole
  - Radiating vessels from the center
  - Arterial pulsation
  - Blanching by central compression
- Distribution
  - Upper portion of body
    - upper thorax—
    - shoulders
    - neck
    - upper arms
  - Rarely on
    - fingers or hands
    - lower extremities very rarely
  - Mucous membrane of nose mouth pharynx
- Significance
  - Diagnostic—chiefly
  - Hemorrhage may result from them

Telangiectasias of
- Nose
- Face and other exposed surfaces
- Common in alcoholics with hepatic disease

Palmar Erythema (Liver Palms)

Mottled redness of thenar and hypothenar eminences and balls of fingers
Plantar erythema may also be present caused by
hyperestrogenism (?) or
expression of increased loss of heat
hypoproteinemia (?)
Not diagnostic when seen in other chronic diseases
Changes in Fingers and Nails
Clubbed fingers
Curved finger nails
Flattening of finger nails
Findings Related to Endocrine Imbala
Males
Loss of body and axillary hair
Pectoral alopecia
Gynecomastia
Testicular atrophy
Females
Breast and
Ovarian changes

55 *Findings Peculiar to Advanced Liver Disease*

Fetor Hepaticus

FETOR HEPATICUS and *nervous system* changes are findings that accompany advanced liver failure regardless of its etiology. They are encountered in various types of cirrhoses as well as acute hepatitis. Fetor hepaticus is characteristic and differs from the uriniferous odor of uremia, the fetor of faulty mouth hygiene or the offensive odor of necrotic neoplasms or Bacillus coli infections. The substance that imparts this odor has not been identified, but it is undoubtedly an amine or several related substances, and may arise from intestinal putrefaction. Alpha methyl piperidine has a similar odor. Urine from normal individuals imparts this odor, and its concentration in the urine is apparently not increased in liver disease.

I have observed it only in patients with severe liver disease in whom there was much other evidence of hepatocellular failure. Therefore it is a serious prognostic sign, but not necessarily a hopeless one, for many patients who exhibit fetor hepaticus recover. Fetor hepaticus is occasionally absent in patients dying from hepatic failure. The intensity and pe sistence of this odor is of some significanc The odor may be very mild, barely detectabl and wax and wane. When it is mild and tra sient, the prognosis need not be poor; howeve if the odor permeates the sickroom, the outloo is poor.

That the origin of this substance re ponsibl for the odor is in the gastrointestinal tract i suggested by the observation that the odo may become more intense during a period o constipation and disappear after a cathartic o a period of diarrhea. I have noticed a similar but not identical odor in patients taking cho line. This odor may be caused by trimethy amine, an intestinal degradation product o choline.

Fetor hepaticus is usually noted in advance hepatocellular failure and, as such, is of help in the differential diagnosis of jaundice. I have detected it in obstructive, post hepatic jaundice only in patients exhibiting signs of the hepatorenal syndrome, and in this stage there is of course considerable parenchymal damage. Since the detection of this sign depend

on the acuity of the olfactory apparatus it may explain why some observers have noticed it in a considerable number of patients with post hepatic jaundice although it is neither as common nor as marked in this type of jaundice

Central Nervous System Findings

Hepatic Coma

The central nervous system disturbances in portal cirrhosis may be divided into two groups One group is associated with and due to chronic alcoholism and will be discussed later under *Complications* the other group of nervous system findings occurs in the advanced stage of all types of advanced hepatocellular failure The nervous system findings vary in their scope character and intensity They usually unravel themselves in a progressive manner and only the advanced stage of this panorama is of grave prognostic significance but even in this stage the outlook is not always hopeless

At the outset changes in personality may be noted An obedient and pleasant patient becomes argumentative sullen critical and disobedient He accuses the physician and nurses of treating him poorly neglecting him not responding to his needs and threatens reprisals for these imaginary misdeeds At the same time he becomes restless difficult to keep in bed and complains of insomnia Drowsiness and lethargy may alternate with the insomnia

Motor changes may also be noted early These include muscular twitching tremors dysarthrias and choreiform movements which resemble those seen in Wilson s disease (Chapter 74) The tendon reflexes are active or hypoactive Ankle clonus develops the plantar reflexes may be normal or abnormal Muscular spasm and increased muscle tonus can be demonstrated The patient lies with his thighs sharply flexed against the abdomen and resists change in posture The rigidity has been referred to as the clasp knife variety but lead pipe and cogwheel rigidity is also noted

Eye changes also occur These include dilated pupil which respond sluggishly to light ophthalmoplegias and jerking of the eyes Nuchal rigidity is occasionally noted when it is marked a complicating central nervous system infection or leptospirosis should be suspected Yawning and hiccoughing also occur These central nervous system changes are almost invariably accompanied by a wretched appetite and complete rejection of food including vomiting Hemorrhagic phenomena also emphasize the gravity of the situation

The mild changes in personality that open this drama may proceed into more drowsiness and finally into stupor and coma Coma may be preceded by delirium and maniacal outbursts which may render the control and protection of the patient extremely difficult The extreme restlessness and violence require restraint but excessive and injudicious use of sedatives may occasionally precipitate prolonged and irreversible coma This is especially true of barbiturates which should never be used in severe hepatic disease

It is important to emphasize that all gradations of nervous system manifestations may occur and these signs may change rapidly and even disappear completely All nervous system deviations are of serious import but coma is the gravest sign of all Recovery however occasionally occurs in a patient who has been in coma Whitfield and Arnott reported three patients with cirrhosis who showed transient coma in several instances with subsequent recovery of consciousness Two of these patients died several months after the first episode of unconsciousness When recovery occurs no residual nervous system abnormalities are detected Electroencephalographic abnormalities are noted during the period of coma these consist of bursts of high amplitude waves with low rhythm This also returns to normal upon recovery

What causes the nervous system signs and symptoms in general and hepatic coma in particular? A satisfactory answer to this puzzling question is not yet available This problem may be subdivided into two subheadings 1 Is there a characteristic anatomical alteration in the brain in severe hepatic disease? 2 Are there specific biochemical alterations which account for the central nervous system disturbances?

Anatomical Changes in the Brain

The question about anatomical alterations in the brains of patients dying from liver disease is discussed in Chapter 74 Although there is some disagreement in this matter most pathologists are inclined to the view that the central nervous system morphological changes in cases of liver disease are nonspecific with the exception of Wilson s disease and kernicterus At times no morphological changes are noted in the brain of individuals dying in hepatic coma These facts along with the rapid reversibility of symptoms and findings the lack of residuals and normal spinal fluid during the process all suggest that the anatomical changes in the brain are not the important factor

Biochemical Changes

Since there are no characteristic morphological changes in the brain the nervous system dysfunction must depend on some biochemical changes First a word about the origin of the biochemical changes which result in hepatic coma It i obvious that the alteration responsible for hepatic coma is failure of the hepatic cell However hepatocellular failure cannot be assumed to be synonymous with hepatocellular necrosis A patient may die from liver cell failure especially in cirrhosis without histologic evidence of recent cellular necrosis Therefore while necrosis may not be present in every case of hepatic coma and there may be no direct relationship between the extent of necrosis and hepatic coma necrosis is very commonly found post mortem In the excellent review of this subject and the report of 18 cases by Walshe 12 patients showed acute necrosis and the 3 patients with long standing cirrhosis likewise showed evidence of necrosis This lack of complete correlation between active necrosis and hepatic coma must at least partially exonerate the disintegrating liver cell protein as the source of the toxic substance even though necrotic liver tissue has been demonstrated to produce toxic effects

There are three possible biochemical deviations which may cause the disturbed internal environment leading to hepatic coma

1 Elaboration or failure of detoxification of a substance toxic to the brain
2 Absence of a substance elaborated by the liver and needed for normal brain function
3 Abnormal intermediary metabolism

While the biochemical abnormalities are legion no single biochemical determination was found by Murphy et al that would distinguish patients in coma from those without coma

The theory of autointoxication ' that a toxic substance originating in the gut by putrefaction enters the blood stream and causes toxic symptoms was in vogue several decades ago This theory was all but ridiculed into oblivion only to be revived again In 1932 Baló and Korpas y produced an encephalitis localized to the caudate nucleus by feeding lean meat to dogs with an Eck fistula This experiment not only pointed to a toxin arising from the intestinal tract and shunted away from detoxification by the liver but implied a deleterious effect from protein The concept of a toxin arising from the intestine is being revived by recent work of Gyorgy and Stokes on the protective effect of aureomycin and other antibiotics in experimental hepatic necrosis The deleterious effect of meat has been implicated by the downgrade course exhibited by dogs with carbon tetrachloride poisoning when placed on a high meat diet (Bollman) Some of these observations resulted in the reduction of meat intake in patients with liver disease for a time Then the pendulum swung over to high protein and hence high meat diets with demonstration of the protective effect of these substances Now it looks like the fickle pendulum of medical opinion is once more beginning to swing away from meat

The disturbance in nitrogen metabolism in grave liver disease and hepatic coma is evidenced by an abnormally high ammonia content of the blood and amino acid increases in the blood and urine While the ammonia content of the blood of patients with hepatic coma is frequently high it may be low or normal therefore this is not a reliable biochemical sign of hepatic coma This variability also implies that the ammonia is not the toxic sub

stance but it may be an expression of the underlying biochemical disturbance In experimental hepatic coma the ammonia content may likewise be high or low Increase in ammonia content of the blood and the development of neurological abnormalities have been noted with the use of ammonia exchange resins and other nitrogenous substances and more rarely with the institution of a very high protein diet (Gabuzda and co workers Phillips and co workers) The last observation must not be accepted without questioning the causal relationship of the high protein diet in the untoward course of the disease It must be remembered that the course of a given case of liver disease is unpredictable and that unexpected and unexplained relapses may occur

The loss of amino acids in the urine and an elevation of blood amino acids are seen in parenchymal liver disease even in the absence of coma or other central nervous system abnormalities The amino aciduria of Wilson s disease is of special interest for it points to the possibility of a causal relationship between the protein metabolic aberration and the combined liver and brain disease However cystinuria was found by Dent and Walshe in even mild liver disease and some of these patients excreted methyl histidine and beta amino isobutyric acid Elevated plasma alpha amino acids are found in patients with hepatic coma In regard to glutamine and glutamic acid the evidence seems to be more pertinent Bollman found glutamine increased in the brain and blood in experimental hepatic coma in the dog The brain glutamine was increased even in the absence of a blood elevation Walshe found the spinal fluid amino acid content increased in patients with hepatic coma The excess of glutamine was especially marked and two patients also showed increases of glutamic acid Methionine sulfoxide was found in the spinal fluid in two other cases

These observations may be quite important in the biochemical explanation of hepatic coma Excessive accumulation of certain amines in part derived from autolysis of liver tissue and in part due to failure of deaminization in the liver may have a toxic effect on the brain Glutamic acid is the only amino acid which is metabolized by the brain The excessive accumulation of glutamic acid and glutamine which is formed from the combination of glutamic acid with ammonia suggests that there is interference in the utilization of this substance by the brain which in turn leads to the disturbance of function noted clinically

The excessive accumulation in the blood of other nitrogenous substance has been discussed in Chapter 63 under *Hepatorenal Syndrome* and need not be elaborated upon further at this point It should be mentioned that in this syndrome the disturbances of consciousness may be due to renal rather than hepatic failure Uremia is accompanied by many disturbances which are akin to those seen in hepatic coma The accumulation of some toxin perhaps structurally (chemically) related to phenol may in part be responsible for hepatic coma Such a toxin has not been identified

Disturbance in carbohydrate metabolism have also been thought to explain the nervous system disturbance Hypoglycemia with its concomitant effect on the central nervous system and its occurrence after hepatectomy is a reasonable suspect However only rarely is hypoglycemia found in heaptic coma and if hypoglycemia were the cause intravenous administration of dextrose should abolish all symptoms Therefore except in rare instances hypoglycemia is not a factor As a matter of fact Walshe mentioned one patient who had an abnormally high glucose content in the cerebrospinal fluid suggesting possible impairment of glucose utilization by the brain

There is some evidence that there is a disturbance in the intermediate metabolism of carbohydrates which may in some way be involved in the production of the nervous manifestations Amatuzio and Nesbitt found elevation of blood and spinal fluid pyruvic acid in patients with hepatic coma This abnormality paralleled the depth of the coma and reduction of pyruvic acid occurred with disappearance of coma The blood pyruvate rises after glucose administration in normal individuals but the rise is much more marked

in patients with hepatic coma (Amatuzio and co workers 1952) Pyruvic acid is metabolized by the normal liver but the liver of patients in hepatic coma is unable to perform this task

Electrolyte disturbances have also been noted in patients with severe liver disease The blood pH is on the acid side Decrease of serum sodium potassium calcium and phosphorus have been noted (Amatuzio and co workers) It is easy to see how the acidosis and hypo kalemia and hypocalcemia would result in nervous system manifestations however they are not responsible for them The electrolyte abnormalities may be successfully rectified but the patient dies in hepatic coma

Findings in Advanced Liver Disease—Summary

Fetor Hepaticus
- Chemical agent unknown—probably an amine
- May originate in the intestines (putrefaction?)
- *When marked and persistent*, a *poor* prognostic sign

Central Nervous System Findings
- Early changes in personality hostile sullen disobedient restless insomniac, lethargy and drowsiness
- Motor changes
  - muscular twitchings
  - tremors, flapping movements of hands
  - dysarthrias
  - choreiform movements
  - muscular spasms
    - clasp knife' rigidity
    - lead pipe and cogwheel rigidity, rarely
    - nuchal rigidity uncommon
  - reflexes
    - active or
    - hyperactive
    - ankle clonus
    - abnormal plantar reflex
- Eyes
  - dilated pupils with sluggish response to light
  - ophthalmoplegias and
  - jerking of eyes nystagmus
- Yawning
- Hiccoughing
- Advanced changes
  - delirium
  - maniacal outbursts alternating with drowsiness—finally
  - coma usually fatal but recovery is *possible*

Pathogenesis of C.N S Signs
- Morphological changes in brain are nonspecific
  - In liver necrosis or hepatocellular failure without recent necrosis
- Biochemical
  1 Toxin originating in the gut?
     - Supported by effectiveness of antibiotics and by increase of C.N S symptoms from nitrogenous substances
     - High ammonia content of blood not invariable
     - Phenol like substance?
  2 Abnormal intermediate metabolism
     - Protein
       - amino aciduria
       - amino acidemia
       - glutamine and
       - glutamic acid increases in brain blood and spinal fluid
     - Carbohydrate
       - pyruvic acid of blood and spinal fluid high

56 Laboratory Features of Portal Cirrhosis

Liver Function Tests

Bromsulphalein Clearance Test

The most valuable test and the one most frequently positive in portal cirrhosis is the bromsulphalein excretion test It is valuable not only because of its sensitivity but because about 50% of these patients are anicteric and this test is not as adaptable to the jaundiced patient It is frequently the only test that is positive and it may be strongly positive when the other tests are equivocal or normal I have seen bromsulphalein retention as high as 40% with other tests being normal In the latent stage of cirrhosis where the symptoms are mild or nonexistent and the physical findings inconclusive the strongly positive bromsulphalein test may aid in directing attention to primary liver disease While the majority of patients with even mild cirrhosis show abnormal bromsulphalein retention the simple 45 minute test may occasionally be negative

There is a dual explanation for the frequency of impairment of bromsulphalein clearance in cirrhosis for not only is there a reduction in the number and capacity of the hepatic cells to extract the dye but the changes in the circulation of the liver reduce the rate of delivery of the dye to the hepatic cells Bradley and his co workers have demonstrated a reduction of hepatic blood flow in various types of cirrhosis with resultant decrease in bromsulphalein extraction and increased arteriovenous oxygen difference The reduced bromsulphalein extraction depends on the reduced hepatic blood flow as well as on the diversion of some of the portal venous blood away from the liver through the collateral channels formed in portal hypertension

The bromsulphalein test is of great help in differentiating hemorrhage from esophageal varices due to cirrhosis from other causes of upper gastrointestinal hemorrhage As was already mentioned hemorrhage may be the first and only sign of cirrhosis While other tests are still negative or equivocal because of the relative intactness of the parenchymal cells the hepatic circulatory disturbance has already reduced the bromsulphalein extraction Hemorrhage from other cause should not impair liver function in the absence of shock therefore I regard a bromsulphalein retention of more than 10% as significant of intrinsic liver disease Zamcheck regards over 16% retention during the acute hemorrhage as signifying liver disease If there is active bleeding while the test is being performed some of the dye will leave the vascular compartment and reduce the positivity of the test

While the chief usefulness of this test is in diagnosis a retention of 30% or more at 45 minutes is a sign of severe impairment and increasing retention is a sign of progression of the disease

Plasma Proteins

A gross disturbance in the plasma proteins is not detected by the Howe technique until the disease is advanced however elevation of the gamma globulin fraction is an early manifestation of cirrhosis (Table 7 p 28) The total globulin may not become elevated at all and the gamma globulin usually *does not reach the* height that this fraction reaches in viral hepatitis and post hepatitic cirrhosis The depression in plasma or serum albumin is a later manifestation than the rise in the gamma globulin An albumin value of less than 3 gm per 100 cc is a sign of impaired liver synthesis of albumin and is seen in about 50% *of patients with* portal cirrhosis Lower albumin values are found in the more serious and more active disease *When the albumin falls* below 2 5 gm per 100 cc ascites and edema are likely to

become manifest (Higgins and associates Post and Patek) However I have seen ascites when the albumin value was above this and no clinical evidence of ascites in other instances with albumin values of 2 0 gm or less

Low and decreasing serum albumin forebodes a poor prognosis A rising serum albumin accompanies convalescence The total protein is likely to be low in portal cirrhosis especially when the cirrhosis is preceded by severe mal nutrition The globulin however is better maintained and falls proportionately less than the albumin The only exception to this is immediately after a massive hemorrhage The result is the reversal of the albumin globulin ratio Since the gamma globulin invariably increases and in the severe disease the albu min drops a marked alteration of the gamma globulin albumin ratio which is normally about 0 35 is a serious prognostic sign (Fig 75)

Flocculation Tests

The flocculation tests like the zinc sulfate turbidity and gamma globulin turbidity tests which depend almost completely on the gamma globulin concentration become positive early and strongly in portal cirrhosis The more com monly used flocculation tests such as the thymol turbidity and cephalin cholesterol floc culation test may remain negative or only mildly positive in advanced portal cirrhosis These tests are more useful in differentiating portal cirrhosis from other types of cirrhosis and other types of liver disease than in the diagnosis of portal cirrhosis The thymol turbid ity which is strongly positive in inflammatory liver disease such as viral hepatitis and post hepatitic cirrhosis is only mildly positive or negative in portal cirrhosis Kunkel found the highest thymol turbidity value in a group of patients with alcoholic cirrhosis to be 16 units with an average of 8 units In non

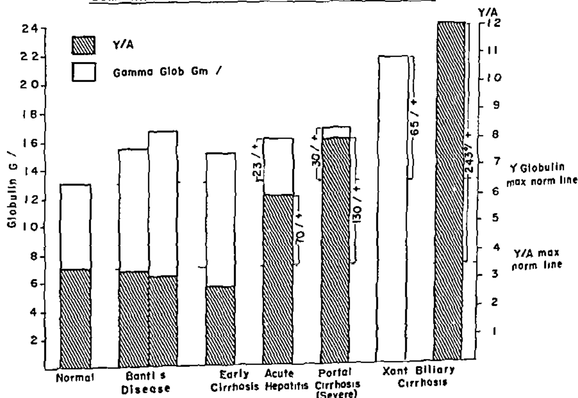


Fig 75 (From Spellberg and co-workers Gastroenterology 14 11 19 0)

alcoholic cirrhosis which probably included biliary and post necrotic cirrhosis these values were 36 and 16 7 units respectively In infectious hepatitis this test was even more strongly positive In this series of cirrhotics the thymol turbidity was consistently negative in 17% of the cases

The cephalin cholesterol flocculation test may also be negative in inactive portal cirrhosis but is more frequently positive than the thymol turbidity in this disease A 2+ or 3+ flocculation test is usually present when the disease is only mildly active and a 4+ flocculation is not infrequently obtained An occasional patient may die from portal cirrhosis with a negative cephalin cholesterol flocculation test This is unusual if the death is due to liver cell failure but both the thymol turbidity and cephalin flocculation tests may remain negative In one series of 198 patients with portal cirrhosis the cephalin cholesterol flocculation test was positive in 90% (Armas Cruz and associates) This is higher than my experience would indicate

The colloidal gold test is positive in the same frequency as the cephalin cholesterol test although occasionally it is positive when the other flocculation tests are negative The colloidal red test is slightly less sensitive in cirrhosis than other flocculation tests

Hyperbilirubinemia

Values of serum bilirubin above normal are slightly more frequent than clinical jaundice nevertheless 40 to 50% of patients with cirrhosis show a normal bilirubin When the bilirubin is elevated this is usually not as marked In Douglass and Snell's series the serum bilirubin was normal in 46% of the cases and in the series of Armas Crus 38 7% were normal in this respect In the former group only -0 5% were clinically jaundiced therefore the hyperbilirubinemia must have been mild in the majority (33 6%) In the Chilean series 3-% had a bilirubin level of 1 1 to 5 mg % 5-% had bilirubin concentrations of 10 to 20 mg and 3 2% over 20 mg % Although the marked hyperbilirubinemias were scarce even in this series they were higher than is usually seen in portal cirrhosis

which brings up the question whether some of these were other than portal cirrhosis The group of patients reported by Baggenstoss and Stauffer is exceptional in this respect since the bilirubin level was the same in the portal and post hepatitic cirrhoses In general it should be emphasized that hyperbilirubinemia is not marked nor always present in portal cirrhosis When present there is clinical as well as morphological evidence of active disease (Ricketts) Increasing bilirubinemia is a poor prognostic sign

The direct prompt reacting bilirubin rises first but as the total bilirubin continues to rise the indirect fraction also rises (Chapter 3) The hyperbilirubinemia is due to retention of bilirubin by the injured parenchymal and Kupffer cells as well as regurgitation from the obstructed intrahepatic bile ducts

Cholesterol and Cholesterol Esters

The total serum cholesterol is usually either normal or depressed in portal cirrhosis Only rarely is this value above normal however in 24% of the cases reported by Armas Cruz and associates there was a cholesterol value above 300 mg % When the cholesterol is elevated the elevation is only slight A low total cholesterol has a poor prognostic connotation The total cholesterol may be elevated during the initial or fatty stage of the cirrhosis and becomes depressed in the advancing disease The cholesterol esters may drop to extremely low levels and along with the decrease in the total cholesterol indicates a poor outcome The cholesterol esters may be normal in the early or inactive phase of cirrhosis this is contrary to our findings of an early drop in cholesterol esters in experimental nutritional cirrhosis (Spellberg and associates)

Alkaline Phosphatase

The characteristic blood value for this enzyme in portal cirrhosis is normal or slightly elevated Slight elevation of the alkaline phosphatase may occur in the absence of jaundice A value above 10 Bodansky units is rare but 8 8% of the patients reported by Armas Cruz had over 10 Bodansky units one patient had 50 Bodansky units A high alkaline phos

phatase is so rare in portal cirrhosis that when it occurs it must be regarded as favoring another diagnosis Patients dying from portal cirrhosis almost invariably show low alkaline phosphatase values (Chapter 8)

Prothrombin Time

The prothrombin time is normal in mild, early and inactive cirrhosis Significant elevation of prothrombin time indicates active and usually advanced disease The hypoprothrombinemia does not respond to vitamin K and is not well correlated with bleeding tendencies I have seen a prothrombin time of 30 seconds or more without hemorrhagic phenomenon while only slightly elevated prothrombin time accompanied serious hemorrhagic tendencies Although marked hypoprothrombinemia is a serious prognostic sign and occurs in nearly all of the fatal cases patients have been known to die from portal cirrhosis in liver failure with a normal prothrombin value

Antithrombin activity is decreased in patients with advanced cirrhosis (p 33)

Urobilinogenuria and Bilirubinuria

Bilirubinuria and hyperurobilinogenuria are present in the jaundiced individuals but increased urobilinogen excretion occurs even in the anicteric patient with cirrhosis Because this pigment may be excreted early in the disease and because of the technical simplicity of the semiquantitative test (Chapter 2 p 11) it may be of great help in establishing a diagnosis Uroporphyrinuria is increased in portal cirrhosis and the relation of concentration of the two isomers is altered (p 1_)

Aminoaciduria

Excretion of abnormal amounts of various amino acids occurs in cirrhosis usually in the advanced stage This has been discussed in various sections of the book Dunn and associates found high amino acid excretion only in active cirrhosis with jaundice The amino acids that they usually found in normal amounts include arginine aspartic acid threonine and tryptophane the amino acids excreted in increased amounts include methionine (Gabuzda and co workers) tyrosine and valine To these should be added cystine, mentioned by Dent and Walshe

Other Laboratory Tests

Urine

Among other abnormalities in the urine are albuminuria This may be due to concomitant or superimposed kidney disease which is discussed in Chapter 65 In marked jaundice the irritation of the renal tubules by the bilirubinuria may contribute to the albuminuria Quantitatively, the albumin lost in the urine is of no importance in contributing to the hypoalbuminemia Cylindruria may also be present and this may consist of bilirubin Pyuria may occur when renal pelvic infections occur

Oliguria is common in severe liver disease and is especially marked during ascites accumulation Polyuria is a sign of improvement of liver function and occurs during disappearance of ascites During the period of oliguria the specific gravity is high but not as high as in other oliguria since there is a reduction in salt excretion The urinary sodium excretion is infinitesimal—less than 5 milliequivalents per 24 hours The chloride retention is not as great therefore there is a sodium and chloride dissociation Potassium excretion in the urine is increased

The sodium retention is also demonstrated in the reduced excretion in the sweat and saliva while the salivary potassium excretion is high giving a fixed high K Na ratio in this excretory product This is well summarized by Eisenmenger These electrolyte abnormalities occur almost exclusively in patients with water retention ascites and edema Water retention can be demonstrated by loading tests described in detail on page 40 (Ralli and co workers 1951 Leslie and co workers 1951)

The abnormalities of urinary hormone excretion in advanced cirrhosis are discussed in Chapter 63 The implications of these abnormalities are also discussed there Goldman and Bassett found the excretion of neutral lipid soluble reducing steroids in the urin markedly reduced to 3 32 mg per 24 hours in patients with cirrhosis and ascites The maximum excretion of these steroids was found to

be in the afternoon and at night Because the hormone excretion paralleled roughly the c ea inire excretion they concluded that the reduction of urinary hormone is dependent on reduced renal filtration This is contrary to the prevalent conception of disturbed hormone elaboration and inactivation

Blood Electrolytes

The serum electrolytes may show marked abnormalities in the advanced stages of hepatic failure and in hepatic coma (p 414) It seems paradoxical that the sodium should be decreased in spite of the decreased excretion The reduction of blood sodium in spite of the reduced renal excretion is explainable on the basis of accumulation of sodium salt in ascitic fluid which is richer in sodium than the serum at times reaching a level of 500 milliequivalents per liter The serum sodium may be lowered d as cally after paracentesis and the re ac cumulation of ascitic fluid Inanition may play a role in lowering the serum sodium

Serum potassium is decreased This is easily explained by the unimpeded excretion and the reduced food intake plays a role in the reduction of all electrolytes This electrolyte is more drastically and more consistently reduced than the sodium in decompensated cirrhosis This is important to keep in mind because of the influence of hypokalemia on other vital functions cardia and nervou systems Other electrolytes may accompany the sodium and potass um in this downward trend with reduction in serum calcium and phosphorus Increased loss in the stools is a factor in the decrease of these electrolytes but I have seen this occur in the ab ence of steatorrhea Ma sive hemorrhage combined with low intake may act synergistically in lowering serum electrolyte Serum pH tends to shift to the acid side in severe liver failure

Nonprotein Nitrogen

Increa e of nonprotein nitr gen in advanced cirrhosis may be partly due to the amino acidemia which ha been alluded to before (p 41) Urea nitrogen decrease o characteristic of hepatectomized animals is rare in man with diffu e necro is Elevation of urea nitrogen occurs its significance is discussed on page 31

Serum Amylase and Lipase

Serum amylase and lipase may occasionally be elevated in hepatic cirrhosis These enzyme abnormalities may complicate the diagnosis when pain and jaundice are present Cummins and Bockus found the amylase elevated in four and the lipase el vated in six of 19 patients with portal cirrhosi Their data suggest that a significant hyperlipasemia may be a poor progno tic sign

Blood Count Blood Volume Sedimentation Rate

The blood picture including anemia of liver disease is discussed in Chapter 67 The anemia i usually normocytic and only occasionally macrocyti (Huang and Wang) The blood volume increase may in part be responsible for the apparent anemia Ferera demonstrated increased plasma volume in 7 out of 10 patients with portal cirrhosis He attributed this increa ed volume to the increased requirement for filling the collateral circulatory bed

The leukocyte count is of con iderable interest in cirrho is since it may be helpful in the differential diagno is A normal or subno mal white count is the rule The leukopenia as was pointed out may be due to hypersplenism and is most frequently associated with spl nomegaly and thro ibocytopenia The low white counts are of help in differentiating cirrhosis and hepatitis from po t hepatic jaundice but occasionally leukocyto is is observed in portal cirrhosis which reduces the value of this diagnostic point In m experience leukocytosi is un ommon but may occur a a preterminal manife tation Armas Cruz and his as ociates found a leukocyte count of 10 000 to 15 000 in 17% and 16 000 to 25 000 in 15% of their ca es This is a disconcertingly high percentage They call it alarm leukocytosis and attribute to it serious prognostic significance Secondary infections are so common in terminal cirrhosis that the leukocytosis may be due to these compli ating factors

The sedimentation rate is increased in mo t ca es of portal cirrhosis (about 85%) Thi is

to be expected since the increased sedimentation rate depends on disturbed plasma proteins. Inactive cirrhosis may show a normal sedimentation rate and increase in this value may *indicate beginning of activity*.

Feces

Occult blood in the stools of patients with cirrhosis may be due to oozing from esophageal varice. Occasionally the stools may be tarry or frankly bloody from a brisk esophageal hemorrhage combined with hyperperistalsis. Occasionally the blood in the stools may be due to the other factors responsible for the bleeding tendency.

Steatorrhea has also been demonstrated in cirrhosis as well as in acute parenchymatous hepatic diseases. The steatorrhea improves with the improvement of liver function. Increased nitrogen loss in the stools (azotorrhea) is rare in cirrhosis. It appears that the fat loss is due to impairment of absorption because of deficiency of bile salt formation. The external pancreatic secretion does not appear to be involved (Gross and associates 1951).

Roentgenography

Esophageal varices. The determination of the exact source of hemorrhage in known cirrhotics and those suspected of cirrhosis requires the painstaking cooperation of the clinician, roentgenologist and endoscopist. Examination of the esophagus roentgenographically using various opaque media should be done routinely in patients with known cirrhosis even before hemorrhage occurs. It is of inestimable help in following the patient and meeting the emergencies when they occur. The use of a thick barium mixture or special preparations on the market such as Rugar is recommended for delineation of esophageal varices. We have recently used sodium carboxymethyl cellulose to thicken the barium mixture and found it effective in demonstrating the scalloping, the widening of the esophageal folds and the characteristic filling defects of esophageal varices (Fig 76).

The demonstration of esophageal varices, which occur in about 20% of patients with cirrhosis, is difficult with a combination of all available techniques including autopsy. Roentgenography, the simplest technique, should be used first and when carefully done should demonstrate most of them, although esophagoscopy gives a higher number of positive results in my experience and the experience of others. Both esophagoscopy and roentgenography may fail to demonstrate varices which cause exsanguination of the patient a short time later. This happened in one of my patients in whom the varices were demonstrated post mortem.

It is important to demonstrate the presence of varices in the stomach. The usual barium mixture may do this (Fig 64) but gastroscopy may be of value in this respect. Although esophageal varices are considered by some as a contraindication against gastroscopy, Moersch recommends it and I am sure I have done it without untoward results.

Roentgenography of the liver and spleen. Flat x rays of the abdomen to demonstrate the size of the liver, I feel, are of no clinical value since their interpretation may be more misleading than palpation and percussion. I have repeatedly seen what looked like the lower edge of the liver shadow at the crest of the ileum when there was no clinical evidence of hepatic enlargement and no hepatic disease. In general the precise size of the liver is not of sufficient value in helping one to arrive at a diagnosis of cirrhosis since normal, large or small livers may be found in this disease.

Demonstration of splenic enlargement would be of greater value since a spleen must be at least twice the normal size to be palpable clinically. Again the flat x ray picture of this organ may be of slightly greater value but is not too accurate. Pressure on adjacent organs by an apparently enlarged spleen is not always corroborated by other facts. The use of Thorotrast has been all but abandoned because of its potential dangers. Recently (1951) Baronchelli and Rossi used a suspension of diiodostearate in glucose intravenously. The suspension consists of particles of 2 microns in diameter and therefore is innocuous from the point of view of embolization. The total amount of the suspension varied between 20 and 35 cc, although there were no signs of intolerance to the drug



Fig. 6 Large esophageal varices extending into the upper third of the esophagus in a patient with portal cirrhosis

they advise the use of cc of the suspension for preliminary testing. The use of 20 cc produced moderate visualization of the spleen but not the liver while 30 to 35 cc resulted in a dense splenic shadow and visualization of the liver. Opacity of the spleen is greatest in three or four hours and the iodine salt disappears from both organs in about 24 hours.

Venous Pressure

The measurement of the venous pressure in one of the accessible veins if it could be cor

Gamma globulin elevated early
Total globulin and gamma globulin not elevated to extent it is in viral hepatitis
Serum albumin decreases later below 2.5 gm % sign of severe disease
Marked disturbance of the gamma globulin/albumin ratio is a sign of serious disease

Flocculation Tests
- Zinc sulfate and
- Gamma globulin turbidity become positive early
- Thymol turbidity and
- Cephalin cholesterol flocculation may be weakly positive or negative
- Colloidal gold test like the above
- Colloidal red less sensitive

Hyperbilirubinemia
- In 50 to 60% of patients
- Usually not marked
- Sign of active disease
- Poor prognostic sign

Cholesterol and Cholesterol Esters
- Total cholesterol normal or even slightly elevated in early fatty cirrhosis
- Esters normal at first
- Total and esterified cholesterol decreased in advanced disease
- Marked decrease—poor prognosis

Alkaline Phosphatase
- Normal or only slightly elevated
- Very high alkaline phosphatase suggests another diagnosis

Prothrombin Time
- Normal in mild disease
- Elevated in advanced disease

Antithrombin Activity
- Decreased in advanced disease

Bilirubinuria and
Urobilinogenuria are common
Uroprophyrinuria is increased
Amino aciduria

Other Laboratory Tests

Urine
- Albuminuria especially in marked icterus
- Cylindruria
- Pyuria
- Oliguria in severe liver disease
- Polyuria during improvement
- Sodium excretion is depressed down to 5 milliequivalents 24 hours
- Potassium excretion increased
- Hormones
  - a 17 ketosteroids decreased
  - b mineral corticoids increased
  - c estrogens increased in male
  - d antidiuretic substance increased in ascites and edema

Blood
- Electrolytes
  - Sodium decreased by loss into ascitic fluid and inanition
  - Potassium decreased due to loss in the urine and inanition
  - Phosphorus and
  - Calcium also decreased
  - pH shifts to acid side
- Nonprotein Nitrogen
  - Elevation primarily due to amino acids and urea nitrogen
- Amylase and Lipase
  - Occasionally elevated
  - Hyperlipasemia may be poor prognostic sign

Blood Count
- Anemia is frequent normocytic and occasionally macrocytic
- Leukocyte count
  - a leukopenia is frequent
  - b leukocyte count may be normal
  - c leukocytosis may be present

Plasma Volume
- Increase may be due to
  - a increased circulatory collateral bed and
  - b water retention

Sedimentation Rate
- Increased in about 80% of patients

Feces
- Occult blood or even
- Gross blood due to bleeding varices or other hemorrhagic phenomena
- Steatorrhea due to impaired absorption
- Azotorrhea uncommon

Roentgenography
- Esophageal varices demonstrated most simply, but not most efficiently by this method
- Liver and spleen
  - a plain film visualization
  - b thorotrast injection
  - c diiodostearate injections

Venous Pressure Determinations
- Superficial abdominal veins may mirror the increased portal pressure

Ascitic Fluid
- Volume may be as high as 20 000 cc
- May be measured by bromsulfalein or radioactive iodine
- Chemical and physical nature
  - a clear
  - b straw colored
  - c low specific gravity
  - d albumin 1–2 gm % may be be higher
  - e Na^+ concentration high above that of serum
  - f antidiuretic substance found in it
  - g free fat—chylous ascites occasionally
- Microscopic examination
  - a to exclude malignant tumor as *cause of ascites*
  - b usually few cells
    - *endothelial and plasma*
    - occasional erythrocyte

Needle Liver Biopsy
- Helps to clarify the diagnosis to classify the type of cirrhosis and exclude primary or metastatic malignancy

57 — Portal Cirrhosis Complications, Causes of Death, and Prognosis

Complications

COMPLICATIONS *in the usual sense are regarded as conditions which follow the development of the primary disease* A host of complications of this type follow in the trail of cirrhosis and are especially likely to occur in the terminal phase and help to seal the fate of the sufferer However there are two conditions seen concurrently with portal cirrhosis not as a part of the disease proper but rather *as the result of a common etiologic factor* These two conditions are (1) nutritional deficiency diseases and (2) chronic alcoholism

Nutritional Deficiency

Stigmata of nutritional deficiency should be sought for in all patients with portal cirrhosis and will be found in a considerable number The frequency of these findings will depend to a certain extent on the social and economic status of the cirrhotics as well as on the frequency and severity of the alcoholic history Those with severe alcoholism even in the better economic classes will show clinical evidence of nutritional deficiency The cirrhosis seen in native populations that subsist on a miserable diet is accompanied by stigmata of malnutrition in the absence of alcoholic excesses

Thiamine deficiency may be evidenced by the polyneuritis formerly called alcoholic neuritis The shooting pains in the extremities the marked tenderness in the *gastrocnemii* the paresthesias and eventual foot and wrist

drop are characteristic Loss of vibratory sense occurs early The edema and cardiac changes of beriberi are rare but may be occasionally encountered

Nicotinic acid deficiency will show up in pellagroid symptoms or true pellagra The diarrhea of the alcoholic or early cirrhotic may be a manifestation of nicotinic acid deficiency The dry scaly encrusted infected skin of vagabond s disease may be due not only to the poor hygiene but injury of the skin from vitamin deficiency Some of the mental disturbances may be on the basis of the nicotinic acid deficiency as well as the alcohol and psychoneurosis Kark showed some correlation between the incidence of pellagra and portal cirrhosis in large municipal hospitals If evidence of nicotinic acid deficiency is suspected mental aberrations may likewise be produced by it rather than by hepatic failure

Riboflavin deficiency may be suggested by cheilosis and magenta tongue Stomatitis and infection and ulceration in other mucocutaneous areas may be due to combined riboflavin and nicotinic acid deficiency Dry scaly skin night blindness and other ocular manifestations may be due to vitamin A deficiency This may be aggravated by the hepatic dysfunction Since parenchymatous liver disease is known to result in impairment of vitamin A absorption night blindness xerophthalmia dryness and scaling of the skin and mucous membrane changes may be due to vitamin A deficiency Atrophy of the tongue which is a common finding in advanced cirrhosis (48% Patek and associates) is a consequence of multiple vitamin deficiencies

Alcoholism

The severe nervous system symptoms of chronic alcoholism at times intrude into the clinical picture of portal cirrhosis creating diagnostic and therapeutic confusion These symptoms may simulate the nervous disturbances seen in hepatic failure the alcoholic stupor alternating with periods of delirium may be diagnosed as hepatic coma I have seen an alcoholic patient in such a condition who was thought to have been rescued from hepatic coma by aureomycin therapy when in reality the intravenous glucose and other supportive therapy had successfully brought him out of alcoholic stupor

Delirium tremens Korsakoff s psychosis and their equivalents and variations can occur in a patient with portal cirrhosis with an alcoholic history The alcoholic tremor differs from the tremor preceding hepatic coma The delirium and maniacal outbursts are more violent in the alcoholic than in the patient with liver failure Convulsive seizures evidence of increased intracranial pressure and hyperpyrexia are likely to occur in the patient with cerebral edema due to alcoholism Abnormal reflexes accompany these neurological manifestations I have been baffled by the selectivity of the end organ effect of alcohol Alcoholics who show violent cerebral symptoms which cause death show minimal hepatic changes such as mildly fatty liver while those with advanced cirrhosis have a minimum of central nervous system involvement attributable to alcoholism

The gastrointestinal symptoms may also develop on the basis of the alcoholic excess rather than the cirrhosis Thus morning nausea and vomiting is characteristic of alcoholic dyspepsia Hematemesis may occur from an alcoholic gastritis The hemorrhage is usually neither so violent nor so persistent as in ruptured esophageal varices

Intercurrent Infection

Infections of various types are accepted as common complications of cirrhosis While they occur most frequently in the late stages of the disease and are associated with the terminal events they may also occur in early cirrhosis in patients in whom the resistance to infection is also below par It is tempting to assume that the lowered resistance to infection is dependent on defective antibody formation associated with the hypoproteinemia

The fallacy of this seemingly logical assumption is recognized immediately when one considers that the gamma globulin which is the carrier of antibodies is actually increased in hepatic disorders This argument can be countered by the concept that the nature of the gamma globulin is altered in liver disease and

hence is not available for antibody *formation* Some direct immunological experiments by Havens and associates demonstrated that patients with cirrhosis and other chronic liver diseases (chronic hepatitis) formed three times as much antibody against diphtheria toxoid as controls without cirrhosis The ability to form *antibodies was not related to age degree of* malnutrition clinical condition of the patient or resistance to intercurrent infection This suggests that other processes are disturbed which result in the lowered resistance to infection

Respiratory infections lead the list these *include bronchopneumonia* lobar pneumonia and pulmonary tuberculosis Other infections are bacteremias of various types tuberculous and nontuberculous peritonitis erysipelas thrombophlebitis pyelonephritis glomerulonephritis cystitis bacterial meningitis parotitis and endocarditis In Ratnoff and Patek s 386 cases bronchopneumonia and nontuberculous peritonitis headed the list of infections with 17 and 12 cases respectively and there were a total of 46 cases or slightly over 10% of infections Douglass and Snell were able to follow a small group (185) of their patients and found that bronchopneumonia caused death of four and peritonitis the death of one of their patients In Patek s recent series 17% of deaths were attributed to infections of various types (Table 61) Jolliffe and Alpert s claim that intercurrent infection is most commonly seen in large municipal series is probably justified Antibiotic therapy and better sanitation and isolation techniques are responsible for the drop in infections in those debilitated patients Thus Blumenau in 1921 noted that out of 126 patients who exhibited evidence of cirrhosis at autopsy 10% had died of tuberculosis and 26% of other infections In a series of cases from the Philippine Islands 22% had chronic *tuberculosis This high incidence undoubtedly* reflects the incidence of tuberculosis in the general population

A case of Bacillu coli septicemia was recently reported by Whipple and Harris this is the only case reported in the English literature in the past twenty years although references to this complication are found in the French and German literature The filtering mechanism of the liver in regard to *bacteria* becomes impaired which may account for the B coli bacteremia The filtering effect of the normal liver on circulating bacteria demonstrated by Beeson and co workers is undoubtedly impaired and accounts for various types of bacteremias

Phlegmonous *inflammation of the intestines* and pancreas is mentioned as a complication of cirrhosis by Pollack and Gerber Greene reported a remarkable case of portal cirrhosis in a patient who died with the following complicating infections bronchopneumonia fibropurulent pericarditis interstitial myocarditis acute cholecystitis *acute hemorrhagic pan*creatitis and acute phlegmonous enteritis Acute ulcerative esophagitis has been described as a complication of cirrhosis (Bartels)

Renal disease and peptic ulcer in relation to cirrhosis are discussed in Chapters 65 and 68

Portal Vein Thrombosis

This is not an infrequent preterminal complication of portal cirrhosis and may set the stage for the exitus Patek and associates attributed death in eight of their 75 patients to portal thrombosis *However among 1 7* instances of portal vein thrombosis only nine were due to cirrhosis (Weir and Beaver) It is much more commonly seen in patients with ascites This complication is usually accompanied by an increase of ascites and a rapid increase in the size of the spleen *(Chap er 49) However this sequence of events does not al*ways occur and I have seen portal vein thrombosis with minimal ascites and only moderate splenic enlargement

Gallbladder Disease

Cholelithiasis being a common condition in *middle* aged individuals can be expected to occur in patients with cirrhosis Its presumed frequency in cirrhotics is not confirmed by the report of Bucalo who found an incidence of cholelithiasis of 13 6% in patients with cir*rhosis as compared with 13* 2% in the control group The bile salt content in individuals with

parenchymatous hepatic damage can be expected to result in cholesterol precipitation and *the formation of cholesterol stones* The associated cholelithiasis complicates the clinical picture Pain under such circumstances may be due to either condition As was pointed out the pain in cirrhosis may be severe The origin of jaundice may likewise be confused and the differentiation of hepatic from post hepatic *jaundice under such circumstances presents insurmountable difficulties*

One should not undertake cholecystectomy lightly in the presence of cirrhosis It is therefore important to evaluate the degree of impairment of liver function or impairment of the health of the patient attributable to the *cholelithiasis Cholecystitis and cholelithiasis* can and do impair the normal liver (p 115) therefore these conditions are bound to impair the abnormal liver The final decision has to take into consideration the severity of the hepatic dysfunction which makes surgery more hazardous Thus surgery is indicated in *cholelithiasis complicating cirrhosis when*

1 there is mechanical interference with bile drainage
2 there are recurrent bouts of cholecystitis
3 the liver failure is not so severe as to preclude surgical recovery

Carcinoma

Primary carcinoma of the liver occurs so much more frequently in the cirrhotic as compared with the normal liver that cirrhosis has been referred to as a precancerous lesion This has been discussed in Chapter 18 Cirrhosis with its sex endocrine imbalance might be suspected to influence development of malignancies in the breast and uterus There is no evidence that cirrhosis either increases or decreases the incidence of carcinoma outside of the liver (Hall and Shao Chien) Metastasis of carcinoma to the cirrhotic liver occurs very rarely Torres found only two instances of metastatic carcinoma to a cirrhotic liver as compared with 300 metastatic carcinomas to normal livers Presumably the poorer circulation of the cirrhotic liver and the fibrous tissue proliferation act as obstacles to the spread of carcinoma

Complications—Summary

Nutritional Deficiency
- More frequent in lower income groups alcoholics and native populations
- Thiamine deficiency
  - polyneuritis
  - shooting pains
  - foot drop
  - loss of vibratory sense
  - edema and cardiac manifestations late
- Nicotinic acid deficiency
  - diarrhea
  - skin changes
  - mental changes
- Riboflavin deficiency
  - cheilosis
  - magenta tongue
  - stomatitis
  - other mucous membrane lesions
- Vitamin A deficiency
  - night blindness
  - xerophthalmia
  - dryness of skin scaling

Alcoholism
- C N S symptoms due to
  - delirium tremens
  - Korsakoff psychosis
  - convulsions
  - tremors
  - reflex changes
- Gastrointestinal symptoms
  - alcoholic gastritis
  - morning nausea
  - hematemesis
  - diarrhea
  - vague dyspepsias

Intercurrent Infection
- Lowered resistance to infection no evidence of defective antibody formation
- Respiratory infections
  - bronchopneumonia
  - lobar pneumonia
  - tuberculosis
- Bacteremias

Peritonitis
Meningitis
Phlegmonous inflammations
intestines
pancreas
Gallbladder Disease
Cholelithiasis—occurs in cirrhosis
may complicate the diagnosis
will raise the question of surgery in the presence of cirrhosis
Carcinoma
Primary carcinoma is common
Carcinoma of other organs are as frequent in cirrhosis as in noncirrhotics
Metastatic carcinoma to liver is rare

Causes of Death

Death of a patient with cirrhosis may be due to the disease process and one of its sequelae or one of the complicating intercurrent infections The two commonest causes of death are *liver failure* and *hemorrhage from esophageal varices* These two causes account for 60 to 80% of the deaths from cirrhosis and compete with each other for first place Thus in the Douglass and Snell group of 85 cases 49 4% died from hemorrhage and 30 6% from liver failure while in Ratnoff and Patek s larger series of 213 cases liver failure was the cause of death in 36 2% and hemorrhage in 25 8% In Fagin and Thompson's 29 patients 15 died from hepatic failure and eight from massive hemorrhage Hemorrhage caused death in 13 (or 17 1%) of Armas Cruz s 76 fatal cases of cirrhosis Presumably a majority of these patients died from liver failure A not infrequent sequence of events is an esophageal hemorrhage followed by death from hepatic failure

Complicating infections are the third most frequent cause of death with respiratory infections heading the list In Ratnoff and Patek s series 16% of the deaths were postoperative Douglass and Snell do not even mention postoperative deaths With the more frequent use of operative procedures in the treatment of portal hypertension there will undoubtedly be a reduction in death from exsanguinating hemorrhage with an increase of postoperative deaths (shunt operations) and deaths from hepatic failure Portal vein thrombosis is listed as a frequent cause of death (see table below) but with the collateral circulation existing in portal cirrhosis it is difficult to see how portal thrombosis can alter the circulation sufficiently to cause death

Principal Causes of Death in 75 Patients with Cirrhosis

	Number of cases in which diagnosis was confirmed at autopsy	Number of cases in which the diagnosis was presumptive
A Cirrhosis		
Cholemia	7	1
Gastrointestinal hemorrhage	10	7
Portal vein thrombosis hemorrhage	4	—
Portal vein thrombosis	4	1
Pneumonia	6	
Peritonitis	4	
Pericarditis	2	—
Bacterial endocarditis hemorrhage	1	—
Glomerulonephritis (uremia)	3	1
B Miscellaneous causes nonhepatic	4	5
Cerebral hemorrhage (3) pyelonephritis gunshot wound pulmonary embolus cardiac failure renal tuberculosis post operative shock		
Total	45	30

A J Patek et al J A M A *138* 543 1948

Prognosis

In spite of our advances in understanding the etiology of liver disease and improved therapeutic approach the prognosis in portal cirrhosis is still gloomy However if we compare groups studied during different periods and therefore with a different emphasis of therapy, or two groups of patients studied by the same observers with and without dietary therapy the conclusion is warranted that modern therapy offers greater hope to the cirrhotic individual As early as 1941 Patek and Post pointed out that 72% of treated patients survived over six months as compared with 57% of untreated patients Fleming and Snell in 1942 likewise reported better response with

the modern dietary therapy which was then coming into vogue

That the prognosis remains far from sanguine is evidenced by the fact that of patients whose diagnosis was made between 1940 and 1944 only 57 5% survived beyond one year and 48 9% beyond two years (Douglass and Snell) Still it is quite an improvement over the series of [illegible] cases treated between 1930 and 1939 and reported by Fleming and Snell Of this group 40% died within three months 58% in six months and 68% did not survive for one year Putting it in another way in the earlier period 32% of the patients survived for one year while in the later period the same number of patients survived for five years At the end of seven years only 19 6% of the traced patients survived and 80 4% died

A comparison of two other series of cases separated by an interval of ten years gives cause for encouragement and hope with the modern therapeutic approach to cirrhosis The table below shows the prognosis in a series of 230 cases followed by Ratnoff and Patek in 194 and a series of 115 cases reported by Patek and associates in 1948 in whom modern dietary therapeutic principles were applied

There is no doubt about the improved outlook in the two periods but a 50% mortality in two years is still very high and a 70% mortality in five years almost equals that from malignant tumors so that results are far from being a cause for exultation However these patients all had ascites and therefore advanced cirrhosis The prognosis is much better for early cirrhosis therefore early diagnosis and appropriate treatment are as necessary here as in other diseases It should be emphasized that portal cirrhosis is an insidious disease and reaches the advanced stage only after many years the duration of the disease from its inception is many years longer than most of the published statistics indicate Moreover the disease is not always progressive and certainly does not progress in a straight line I have seen the diagnosis made unexpectedly at surgery the patient then lived for ten years or longer without apparent progression of the disease with death finally occurring from an unrelated condition

Signs indicating poor prognosis are

1 Hematemesis from esophageal varices
2 Ascites
3 Jaundice especially if progressive
4 Fever
5 Hypoalbuminemia (below 2 5 gm %) persistent
6 High and increasing gamma globulin/albumin ratio
7 Moderate hypoprothrombinemia
8 Low and falling antithrombin titer

Signs indicative of grave prognosis

1 Severe cerebral symptoms and coma
2 Marked hemorrhagic phenomenon
3 Marked hypoprothrombinemia
4 Marked and persistent fetor hepaticus

Prognosis of Bleeding Varices

It is especially appropriate to indicate the gravity of bleeding esophageal varices in view of the present concerted effort to treat this symptom About half the patients with massive hemorrhage from esophageal varices die within one year of the initial hemorrhage—this in spite of dietary therapy but without specific therapy directed to the varices (Chapter 50) As serious as this episode is in the life history of a patient with cirrhosis the outlook in this respect has improved with greater availability of blood and the salutary effect of the dietary regimen In Patek and Ratnoff's 194- series 40% died within one month many from the first hemorrhage and another 30% or a total of 70% in the first year The first year is critical if the patient survives one year the outlook becomes better However 80% of those with hematemesis died within seven years

Prognosis of Ascites

The presence of ascites in a patient with cirrhosis is a poor prognostic sign hence the designation decompensated cirrhosis The following table lists Patek's mortality statistics summarizes data on cirrhotics with ascites

Per cent of survival at end of	Ratnoff and Patek 194	Patek et al 1948
1 yr	[illegible]9%	65%
2 yrs	1[illegible]%	50%
5 yrs	7%	30%

It indicates the improved outlook with modern therapy but still emphasizes the gravity of this finding 50% of patients having died at the end of two years In Douglass and Snell s series the survival rate of patients with cirrhosis was as poor as in Patek s 1942 series that is only 37 1% survived for one year The experience with ascites at the Mayo Clinic was no better in 1950 with the modern form of therapy than it was in 1931 as reported by Chapman and associates The three year survival for patients with ascites was 25% in 1931 and 23% in 1950

Ascites more so than esophageal varices is dependent upon disturbed liver function many facets of which contribute to its formation Therefore accelerated regeneration of functioning parenchyma and reduction of degeneration and fibrosis should abolish this ominous finding Many patients with ascites and even those who have required repeated paracenteses may get rid of the ascites with persistent therapy (p 579) Fifty per cent of Patek s group of patients showed disappearance of ascites therefore one should not be unduly pessimistic even in its presence

Prognosis of Jaundice

Jaundice in portal cirrhosis is a poor prognostic sign however if it is mild and not progressive it should not be looked upon with alarm Transient mild jaundice may occasionally occur in early cirrhosis When jaundice is persistent and progressive it is accompanied by clinical laboratory and morphological signs of severe liver damage and hence denotes a poor prognosis Douglass and Snell s group of jaundiced patients had a mortality rate of 53% in the first year and none survived for seven years In Patek s 1948 series jaundice disappeared in 75% of cases within two months With more active therapy the majority of patients with this sign of hepatic failure should show improvement

Other clinical signs indicative of a poor prognosis are listed on page 429 Fever is a sign of progressive liver failure while defervescence is an early sign of improvement Hepatic coma as well as hemorrhagic phenomena are grave signs and in most instances forebode a fatal outcome

Laboratory Tests and Prognostic Significance

The serum albumin concentration is a valuable prognostic index An albumin concentration of less than 2 5 gm per 100 cc is indicative of serious functional impairment of the liver Marked alteration of the gamma globulin/albumin ratio likewise indicates a poor prognosis Mild hypoprothrombinemia may occasionally occur in moderately advanced portal cirrhosis with sufficient reserve and regenerative capacity for recovery however marked hypoprothrombinemia usually indicates progressive hepatic failure A low and falling antithrombin titer likewise indicates a poor prognosis

Prognostic Value of Histologic Changes

The value of needle biopsy in the diagnosis of cirrhosis is undisputed There is a divergence of opinion about its prognostic value Some deny that there is sufficient correlation between the histologic findings on the one hand and clinical and laboratory picture on the other hand to attribute prognostic significance to the microscopic picture (Patek and associates 1948 Rose and Post 1950) While I feel that needle biopsy is not nearly so valuable in predicting the prognosis in portal cirrhosis as it is in chronic hepatitis and post hepatitic sequelae it is nevertheless of some value in portal cirrhosis

Since progressive hepatic failure is due to a large extent to hepatocellular degeneration while improvement and recovery depend upon effective regeneration the liver biopsy should contribute to the determination as to which process has the upper hand The problem of correlation between histology and function is discussed in Chapter 11 The observations of Popper and his associates indicate that certain histologic changes are indicative of active hepatic disease Ricketts noted histologic evidence of parenchymal degeneration in patients with clinically active cirrhosis Hepatocellular degeneration and necrosis suggest a poor prognosis Round cell infiltration indicates activity of the disease In serial biopsies decrease of fatty infiltration bile stasis and fibrous tissue and increased regeneration give histologic evidence of improvement

58—Biliary Cirrhosis Classification, Etiology, Pathogenesis, and Pathology

Classification

Definition

The second large group of the hepatic cirrhoses can be designated as biliary cirrhosis or hypertrophic cirrhosis As has been pointed out (p 364) the term hypertrophic may be confusing and should be abandoned In its atypical form biliary cirrhosis may be confused with portal cirrhosis and has been designated as mixed cirrhosis it has the following distinctive features

1 Etiologically it is related to interference with bile flow
2 This type of cirrhosis is usually seen in women and children and is rare in men
3 Jaundice frequently of marked degree is invariably present
4 Pruritus is almost always present at some time during the course of the disease
5 The liver remains enlarged even terminally
6 Findings indicative of hepatic dysfunction may be minimal or absent for a long period of time
7 Ascites is a very late manifestation
8 Hyperlipemia hypercholesterolemia and xanthomas are distinctive features of some of these patients

Synonyms and Types

The terms used in reference to biliary cirrhosis are hypertrophic cirrhosis Hanot s cirrhosis Charcot s cirrhosis cholangiolitic cirrhosis cholangitic cirrhosis cholangiostatic cirrhosis pericholangiolitic cirrhosis and xanthomatous cirrhosis *These terms are not* strictly synonymous but refer to special types of biliary cirrhosis Hypertrophic cirrhosis is the only one of these terms that is used with reference to the entire group and hence synonymously with biliary cirrhosis Hanot s cirrhosis and Charcot s cirrhosis have also been used to designate the entire group but originally they were intended to designate only the primary biliary cirrhosis

Cholangiolitic cirrhosis is the term used to designate the type of biliary cirrhosis in which the small intrahepatic bile ducts cholangioles are involved while the term *cholangitic* cirrhosis refers to involvement of the larger bile ducts Pericholangiolitic cirrhosis is similar to cholangiolitic cirrhosis in connotation but the term was used by McMahon and Thannhauser to designate xanthomatous cirrhosis Xanthomatous cirrhosis or xanthomatous biliary cirrhosis is a useful descriptive term for biliary cirrhosis with cutaneous xanthomas

Classification

A useful classification that takes into consideration the level of the bile duct obstruction as well as the chief accessory factor involved in the hepatic injury is (1) primary biliary cirrhosis (hepatic biliary cirrhosis) and (2) secondary biliary cirrhosis (posthepatic biliary cirrhosis) Secondary biliary cirrhosis may be subdivided into (a) cholestatic and (b) cholangitic cirrhosis

Primary biliary cirrhosis refers to an intrahepatic bile duct obstruction as the cause of the cirrhosis while secondary biliary cirrhosis refers to an obstructing agent acting on the extrahepatic biliary tree The designations primary and secondary are objectionable and confusing All types of biliary cirrhosis are *secondary* to some agent that produces the obstruction of the biliary passages the only difference between the hepatic obstruction and the posthepatic obstruction is that in the

former type the causative agent is not always well defined or determined with certainty and usually has the nature of an *inflammatory process (virus hepatitis)* I *therefore propose* the terms hepatic biliary *cirrhosis for the type in which the obstruction is in the liver* (hepatic) and posthepatic biliary cirrhosis *for the type in which the obstruction is post hepatic*

The terms cholangiostatic and cholangiolitic reflect respectively the mechanical pressure exerted by the duct obstruction and the superimposed *infection involved in the production* of the hepatic lesion It is obvious *that in the cholangiolitic type infection exists* in addition to the mechanical obstruction and therefore there is no pure itic type although there can conceivably be a pure static type in posthepatic obstruction without superimposed infection

Etiology

Incidence

Biliary cirrhosis is much less common than portal cirrhosis Its frequency according to material already published varies a great deal and depends on the type of biliary cirrhosis (its definition) and the predominant age and sex of the hospital population Karsner cites the incidence of biliary cirrhosis among all types *of cirrhoses to be as high as* 37 6% in one group In his own group 18% were of the biliary type and he approximates that the average is about 9% *of all cirrhoses On a large* male medical ward I have seen three cases in one year that conformed to the diagnosis of biliary cirrhosis Moschcowitz collected 45 cases of biliary cirrhosis in a period of 25 years at the Mount Sinai Hospital in New York

The relative incidence of the various types of biliary cirrhosis in the order of frequency is (1) *secondary biliary cirrhosis* (posthepatic) (2) primary biliary cirrhosis (hepatic) and (3) xanthomatous *biliary cirrhosis* The xanthomatous type may be either primary or secondary The rarity *of this form of biliary* cirrhosis is illustrated by the fact that only 92 cases were reported in the world literature over a period of 100 years (1851–1950) The e were described by Ahrens and co workers

Compare this with 45 cases of biliary cirrhosis *of all types found in one institution in* 25 years In Moschcowitz's series of 45 cases only 6 were of the primary (hepatic) variety the re t were of the secondary or posthepatic type The *primary nonxanthomatous type* is not very rare This can be deduced from the report of 10 cases from the University of Chicago (Ricketts and Wissler) over nearly a 20 year period and 8 cases from the University of Minnesota within several years *Primary biliary cirrhosis* (cholangiolitic cirrhosis) should be expected to *increase in frequency* because of the increase of viral hepatitis to which it seems to be a sequel

Age

Patients with biliary cirrhosis may be found from birth to advanced age from a few minutes to over 60 years This extremely wide age *spread is confined to patients with extrahepatic* obstruction because of congenital bile duct *malformations* The *primary (hepatic) type* does not begin until after the age of 20

Sex

The preponderance of women with this disease is one of its characteristic and intriguing features This predilection for women is especially marked in the xanthomatous cirrhosis with intrahepatic obstruction Of the 25 patients reported in the literature and collected by Ahrens and co workers all but 4 were *women while all 8 of their own were women Nonxanthomatous hepatic biliary cirrhosis* (cholangiolitic cirrhosis) *which is a sequel to* viral hepatitis is *not* infrequent in men since the primary disease does *not show a sex* predilection

Secondary (posthepatic) biliary cirrhosis is also commoner in women since gallbladder disease and its postoperative complications are commoner in women

Heredity and Racial Factors

Heredity plays no part in the etiology of *biliary cirrhosis* Hypercholesteremia is a hereditary trait but primary hypercholesteremia is not associated *with biliary* cirrhosis It is in e esting to note that in one study familial hypercholeste emia *was 10 times as frequent* in

Jewish as in non-Jewish families with approximately equal number of families studied (Adlersberg et al.), while Ahrens and co-workers report that 7 of their 12 patients with biliary cirrhosis were of Jewish extraction. The etiological significance of the last observation is minimized because the group came from an area with a large Jewish population.

Factors Implicated in the Causation of Biliary Cirrhosis

Primary Type (Intrahepatic obstruction)

This type of biliary cirrhosis has been called primary because the exact cause is considered to be unknown. While this may be true in many or most persons, it is not true of all of them. The two groups of noxious agents that may produce injury of the intrahepatic cholangioles are infections and toxins.

Viral hepatitis. One of the chronic sequelae of infectious and homologous serum hepatitis (viral hepatitis) is a chronic cholangitis that may lead to cholangiolitic cirrhosis. The cases reported by Watson and Hoffbauer trace this sequence clearly. I have seen this evolution in one case and other cases of a similar type have been reported (Ricketts). The progression from acute hepatitis to biliary cirrhosis may be observed more frequently in the future because of the awareness of this evolution and because of the greater frequency of hepatitis.

Cholangitis lenta. The term cholangitis lenta has been used synonymously with biliary cirrhosis but without justification. This cholangitis was originally described by Schottmuller in 1921 as a complication of a Streptococcus viridans biliary tract infection. While such infection may eventually lead to chronic intrahepatic biliary obstruction and biliary cirrhosis, it must be an exceedingly rare event.

Obliterating cholangitis. Intrahepatic cholangitis with eventual obliteration of the ducts has been described by Klemperer (1937). When this process continues for a prolonged period of time, it may eventually lead to biliary cirrhosis. Recently Rachmilewitz reported five patients with chronic intrahepatic cholangitis; in some of these fibrous tissue proliferation occurred.

Congenital atresia of intrahepatic bile ducts. Atresia of intrahepatic ducts may occur in conjunction with extrahepatic duct anomalies or as isolated abnormalities. Ahrens and associates reviewed cases found elsewhere in the literature and presented two of their own. Their two cases and two others previously reported showed no recognizable biliary epithelium in the portal spaces. McMahon and Thannhauser reported xanthomatous cirrhosis in a 10-year-old boy with a complete absence of small and large interlobular bile ducts. They propose the term congenital acholangic biliary cirrhosis.

Toxins. Some toxins (Chapter 24, p. 172) damage the intrahepatic bile canaliculi and thereby cause an intrahepatic biliary obstruction. The drugs that are known to produce such a change are the arsenicals and testosterone. Usually the intrahepatic biliary obstruction is not protracted, and the patient's recovery is complete. Jaundice and biliary obstruction, however, may continue for a long period and result in biliary cirrhosis. Such a development is reported by Stolzer and co-workers. Their patient developed xanthomas 10 months after the onset of jaundice. The presence of biliary cirrhosis was proved by liver biopsy.

Endocrine factors. None of the factors discussed so far appeared to be responsible for biliary cirrhosis in the patients studied by Ahrens and associates. The lack of definite causes in many instances forces the conclusion that the disease is idiopathic and makes one look elsewhere for an explanation. The great frequency of the primary disease in women directs attention to possible derangement of the internal secretions. Ahrens and his associates evaluated the endocrine aspects of their patients and found no clue of importance. Ovarian function was not unusual in any of these women prior to onset of the disease. Menstrual disturbance occurred in some of the patients after the disease was established, but these disturbances were in no way different from those seen in women with other chronic diseases or in women with portal cirrhosis. Vaginal smears show some deviations from the normal but none peculiar to this disease.

There is likewise no evidence of disturbed adrenal activity as measured by 17-ketosteroid

excretion glucose tolerance tests and eosinophil response to ACTH Also there is no evidence of disturbed thyroid activity to account for the disease process The role of the thyroid in controlling the blood level of cholesterol might lead one to expect an abnormality in this function in xanthomatous cirrhosis with hypercholesterolemia but even this relationship is not upheld by the facts

Secondary Type (Posthepatic)

There is no mystery about the causes of secondary biliary cirrhosis (posthepatic) In these patients a posthepatic obstruction of the biliary tree is present Any condition that can cause and maintain such an obstruction can produce biliary cirrhosis The causes of posthepatic jaundice listed on page 91 may also be applied to biliary cirrhosis To reiterate briefly carcinomas of the pancreas the duodenum the papilla of Vater the common bile duct the hepatic bile duct and the gallbladder can cause biliary cirrhosis

One might presume that a patient with a malignant neoplasm would not survive long *enough to allow* biliary *cirrhosis to develop* but this is not so In 12 of the 45 patients studied by Moschcowitz biliary cirrhosis was *due to obstruction of the common bile duct* by a carcinoma of the head of the pancreas Xanthomatous biliary cirrhosis due to carcinoma of the duodenum was recently reported in a 22 year old man (Heaney et al) Carcinoma of the papilla common duct carcinomas and metastatic neoplasms may obstruct the common duct and result in biliary cirrhosis Carcinoma of the gallbladder usually does not produce marked posthepatic jaundice but it may occur (p 118) and may result in biliary cirrhosis as well Non neoplastic lymph node enlargement may also obstruct the common duct and produce biliary cirrhosis Xanthomatous biliary cirrhosis in a young Negro with sarcoidosis was recently reported by Foxworthy and Freeman Benign neoplasms may also contribute to the production of biliary cirrhosis

Obstruction of the common duct by benign lesions is the commonest cause of secondary biliary cirrhosis Calculous obstruction of the common bile duct heads this list in spite of the fact that the obstruction is usually incomplete Postoperative strictures *of the common* duct are another frequent cause Congenital atresia of extrahepatic bile duct may be due to either *a congenital anomaly or a prenatal* inflammatory process occluding the duct Congenital atresia is commoner than usually *realized and is frequently* accompanied by occlusion of intrahepatic bile ducts as well (Ahrens et al 1951)

Pathogenesis of Xanthomatous Biliary Cirrhosis

The genesis of xanthomatous lesions of the skin were interpreted by Weidman and his associates as being due to an uptake of cholesterol by phagocytic cells after a local injury Hypercholesteremia preceded the formation of xanthomas This opinion was based on clinical observations that in patients with hypercholesteremia xanthomas developed at the site of scars burns and herpes zoster lesions and in the animal experiments performed by Anitschkow it was demonstrated that there was *localization of xanthomas in healing* experimental abscesses produced in hypercholesteremic rabbits According to this theory *hypercholesteremia precedes the development* of xanthomas

Thannhauser and Magendantz (1938) originally *maintained that xanthomas and hyper* cholesteremia (hypercholesteremic xanthomatosis) were expressions of deranged lipid metabolism that they *developed concurrently* and that the jaundice and biliary cirrhosis were secondary to the development of *xanthomatous* lesions in the bile ducts *which resulted in* obstruction of the ducts This opinion was based on the review of old autopsy specimens presented by Fagge *and Moxon that demon*strated foam cell xanthomas in the bile ducts This concept is now considered erroneous and was abandoned by *Thannhauser* who with McMahon studied tissue from seven patients with biliary cirrhosis and xanthomas and found no biliary xanthomas They found instead an inflammatory process around the small and the medium sized bile ducts with intralobular bile stasis They concluded that the hypercholes

terolemia was secondary to the bile duct obstruction and that the obstruction was due to a pericholangiolitis They therefore proposed the term pericholangiolitic biliary cirrhosis with xanthomatosis

It is generally accepted now that hypercholesterolemia is a direct result of biliary obstruction That interference with the flow of bile causes an increase of blood cholesterol is demonstrated by animal experiments (p 34) as well as by clinical observations The increase of blood cholesterol is due to retention of cholesterol from the regurgitated bile as well as other factors The liver not only excretes cholesterol but also synthesizes it as evidenced by the drop in total cholesterol in cases of severe hepatocellular damage Under the stimulus of biliary obstruction the synthesis of cholesterol by the liver may increase The liver may also destroy cholesterol (Bailey and Freeman) but with the mild damage caused by biliary obstruction the ability of the liver to destroy cholesterol may decrease and contribute to its accumulation in the blood stream

The rise of serum lipids results in the accumulation of lipid deposits in the form of xanthomas Ahrens and Kunkel concluded from their study of 18 patients with primary biliary cirrhosis that there is a direct relationship between the degree and duration of the hyperlipemia and the formation of xanthomas They found that in patients with serum lipid levels of above 2 000 mg per 100 cc diffuse xanthomas developed that in those with lipid levels of below 1 300 mg no skin lesions developed and that in the intermediate group only xantholasmas developed

Since both hepatic and posthepatic biliary obstruction will result in hyperlipemia xanthomas develop in both the primary and secondary biliary cirrhoses and hence there may be a primary xanthomatous biliary cirrhosis or a secondary xanthomatous biliary cirrhosis Shay and Harris refer to primary biliary cirrhosis as hepatocellular hypercholesterolemic cirrhosis because it originates from a condition associated with primary parenchymal damage while the secondary type they feel is a true biliary cirrhosis with biliary obstruction as the dominant defect In posthepatic biliary obstruction intrabiliary xanthomas occasionally develop while in primary hepatic biliary obstruction these peculiar lesions do not develop in the ducts

Any biliary obstruction has the potentiality of causing xanthomas depending on the height and duration of the hyperlipemia For this reason the term pre xanthomatous phase has been proposed to refer to biliary cirrhosis before xanthomas develop (Ahrens et al 1950) When xanthomas develop the xanthomatous phase is reached and since xanthomas occasionally disappear this phase can be referred to as a postxanthomatous

Pathogenesis of Xanthomatous Biliary Cirrhosis—Summary

Obstruction to Outflow of Bile

- **A Site**
  - **1 Intrahepatic**
  - **2 Posthepatic**
- **B Hypercholesterolemia results from**
  - **1 Regurgitation of cholesterol from retained bile**
  - **2 Increased synthesis of cholesterol by liver cells**
  - **3 Reduced destruction of cholesterol by liver cells**
- **C Hyperlipemia 2 000 mg per 100 cc or above results in the development of diffuse xanthomas or the xanthomatous phase**
- **D Hyperlipemia 1 300 to 2 000 mg per 100 cc results in xanthelasmas**
- **E Hyperlipemia below 1 300 mg per 100 cc causes no xanthomas pre xanthomatous phase**

Pathogenesis of Biliary Cirrhosis

The pathogenesis of biliary cirrhosis revolves around biliary obstruction which is a feature of all its forms The site of the obstruction intrahepatic or posthepatic and the presence or absence of infection have some effect on the development of the morphological alterations thus cholestasis is always present but cholangitis may develop after posthepatic obstruction has taken place In the intrahepatic obstruction the cholangiolitis or pericholangi

olitis is primary and is followed by the cholangiostasis

Cholestatic Changes

The morphological change in the liver following simple obstruction of the extrahepatic ducts is easier to delineate first because this is the only type that can be divorced from infection and second because it can be easily produced and observed experimentally From studies of clinical as well as experimental material it is well established that stasis without infection can cause hepatic damage The result of aseptic experimental obstruction of the common duct was elucidated long ago by Richardson (1911) in rabbits and McMahon and associates (1929) in guinea pigs They noted a dilatation and tortuosity of bile ducts undoubtedly caused by increased intraductal pressure It is surprising that within 24 hours after duct ligation necrosis of hepatic cells in the periphery of the lobule took place and that lymphocytes and macrophages invaded these necrotic areas The necrosis extended from the periphery to the center of the lobule These necrotic areas were repaired by fibrous tissue that distorted the architecture and resulted in cirrhosis

Extensive dilatation of the biliary passages in patients with common duct obstruction due to a ston or carcinoma is well known Counseller and McIndoe called attention to these changes in 1926 and pointed to them as the cause of parenchymal atrophy and necrosis

Is the massive retention of bile by the hepatic cells or the increase of hydrostatic pressure responsible for the hepatocellular injury? The evidence favors the mechanical factor as the dominant cause The cells that are most deeply stained with bile pigment are not the ones that show the severest necro is and there is no evidence that bilirubin is toxic On the other hand increased intraductal pressure can cause compression of the vascular channels local ischemia and ischemic necrosis of the hepatic cells The possibility has not been excluded that some other excretory product of the liver (with its numerous detoxifying functions) may be toxic to the liver cells when it is retained

The rate of development of the advanced stage of biliary cirrhosis is of importance from a clinical point of view Observations in animals are of little help in this respect for they cannot be applied directly to the longer life span of man Moschcowitz made observations on autopsy material correlating the morphological change with the duration of the jaundice

First stage This stage was observed in persons in whom obstruction of the common duct due to a stone or carcinoma was of several weeks duration There is infiltration of portal spaces by lymphocytes and a few polymorphonuclear leukocytes and plasma cells This infiltration does not involve the entire portal space and the exudative process is usually confined to the interlobular septa at the point at which the intralobular bile canaliculi join the interlobular bile ducts As time progresses there is an increase in size of the portal space and increased vascularization Atrophy of hepatic cells is seen adjacent to the areas of infiltration and fibroblastic infiltration In this stage the normal morphology of the liver is preserved the relationship between the central vein and portal space is unchanged

Second stage The structural changes that characterize the econd stage were seen in patients with jaundice that varied from 11 weeks to 14 years in duration The fibrous tissue is more extensive and more mature The fibrous tissue septa fuse to form pseudolobules and distort the normal relationships Newly formed bile ducts are seen that may have a lumen and the lumen may be filled with bile thrombi Focal necrosis is seen but is uncommon

Third stage This stage is marked by further advance in the process and the formation of a full blown biliary cirrhosis The patients in this group dated the onset of jaundice several years previously The fibrous tissue proliferation is more marked in this stage than in the first two The architecture is completely altered by intralobular perilobular and periportal connective tissue The relationship of the central vein to the lobule is completely lost and no normal lobules are seen Vascular connective tissue forms communications between the thickened hepatic veins and portal spaces Marked lymphocytic infiltration of the bile ducts is found Numerous newly formed bile ducts are seen

and many are plugged with bile thrombi There is an abundance of bile pigment in the paren chymal and Kupffer cells Focal necrosis and regeneration vary in incidence and may not be conspicuous Bile necrosis (bile lakes) is a common feature of the posthepatic obstruction

Time is not the only factor that determines the progression of the hepatic lesion in biliary obstruction The completeness or intermittency of the obstruction influence the rate of develop ment of biliary cirrhosis In intermittent ob struction and incomplete obstruction there fore the advanced stage will take longer to develop It is more than likely that other factors that produce hepatic injury play an accessory role in the progression of the lesion Infection arising in the obstructed biliary tree when present unquestionably plays a role in develop ment of the architectural alterations

Cholangitic Changes

When inflammatory changes take place in posthepatic obstruction they are secondary to the obstruction and superimposed on the changes described above The exudative process is more marked and consists predominately of polymorphonuclear leukocytes These cells are seen not only around the bile ducts but also in their lumen Both cholangitis and cho langiolitis may exist depending on the size of the ducts involved Miliary abscesses may form around the bile channels The infection will obviously aid in obliteration of the ducts and if the obstruction is ameliorated as occurs in calculous obstruction by movement of the stone or readjustment of the terminal end of the duct the inflammatory exudate in and around the ducts may maintain the obstruc tion If the inflammatory process is virulent the result is formation of multiple abscesses rather than development of biliary cirrhosis A low grade inflammation exaggerates the ob struction and the bacteria both directly and indirectly contribute to hepatocellular damage Clinical and laboratory signs of hepatic dys function will occur sooner in the presence of a cholangitic process

Primary Intrahepatic Obstruction

The evolution of primary intrahepatic ob struction undoubtedly differs from time to time and depends on the primary disease that precedes it In the instances in which this dis ease follows a viral hepatitis evidence of hepatocellular necrosis may be found Paren chymal changes however may be minor or absent since biliary (cholangiolitic) cirrhosis most frequently follows cholangiolitic hepatitis In cholangiolitic hepatitis the inflammatory process involves chiefly the intrahepatic bile ducts the parenchymal cells are spared Most of these cases are idiopathic in origin and even in those that follow a known disease or noxious agent and at the late stage at which most of these livers are seen the morphological changes are undistinguishable from those that occur in the third stage of posthepatic biliary cirrhosis (Moschcowitz) McMahon and Thannhauser s description of their patients with xanthomatous biliary cirrhosis is in keeping with this view point They state that at the beginning the process of round cell infiltration is centered around the terminal bile ducts and is confined to the portal spaces From there the lesion spreads out intralobularly and perilobularly Vascular granulation tissue spreads out from the portal spaces and when sufficiently abun dant results in pseudolobulation and distortion of the normal lobular relationship Because this is an intrahepatic lesion liver cell degener ation and necrosis are commoner and signs of regeneration are more abundant

Pathogenesis of Biliary Cirrhosis—Summary

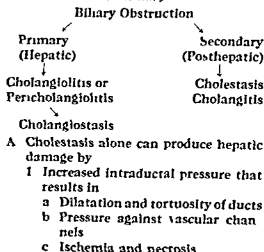




Fig 77 A Biliary (cholangiolitic) cirrhosis. Needle biopsy X [illegible] showing middle of lobule [illegible] cells surrounded [illegible] thick band of fibrous tissue [illegible] marked lymphocytic [illegible] and [illegible] cell infiltration [illegible] proliferation of bile [illegible]

B Showing (X [illegible]) the bile [illegible] and hepatic cells [illegible] with [illegible] bile canaliculi [illegible] A

The patient was a [illegible] year old female who developed [illegible]

(3) less extensive fibrous tissue proliferation
(4) more abundant inflammatory reaction
(5) less necrosis and degeneration
(6) less hepatocellular regeneration and
(7) no fatty metamorphosis

Bile necrosis (bile lakes) may be found in both primary (intrahepatic) and secondary (posthepatic) biliary cirrhosis but it is commoner in the latter. In intrahepatic obstruction the larger bile ducts are empty and bile duct obliteration may be so marked that the number of smaller bile ducts is reduced. In posthepatic biliary cirrhosis the larger bile ducts are conspicuous because they are dilated and filled with bile and the proliferation of smaller bile ducts is marked.

In the larger bile ducts hyperplasia of the epithelium may occur and especially in secondary (posthepatic) biliary cirrhosis (Shay and Harris) macrophages filled with lipid material (foam cells and/or xanthoma cells) may be found in the submucosa of these ducts. In the primary type the inflammatory process involves primarily the smallest bile ducts and produces an intralobular biliary stasis (Figs 77 and 7[illegible]). In this variety hepatocellular changes both degeneration and regeneration are common.

Xanthoma Tuberosum

The orange yellow tumors that are a characteristic feature of xanthomatous biliary cirrhosis are composed of the peculiar foam cells in a fibrous tissue network. The foam cell is a histiocyte filled with lipid chiefly cholesterol. These cells vary in size and contain an abundance of cytoplasm and one or two nuclei. The lipid is distributed in small droplets in the cytoplasm so that when the fat is washed out with alcohol it leaves not vacuoles but a fine meshwork which gives the cell its foamy appearance (Fig [illegible]8). These cells stain yellow or red with Sudan III and pink with Nile blue sulfate. The cholesterol esters produce double refraction of polarized light (Thannhauser).

Microscopically the spleen shows fibrosis and congestion similar to that in portal cirrhosis. In the xanthomatous type the spleen may show foam cells even though they are absent in the liver.

Atheromatous changes in the arteries may be marked as an expression of prolonged hypercholesterolemia. The pulmonary arteries may show marked atheromatous changes even in the absence

jaundice 6 months before death. The disease followed a rapid progressive downhill course. The liver was enlarged and firm chiefly the left lobe. Ascites finally developed. Liver function tests 5 days before death: Serum bilirubin [illegible] mg%. Alkaline phosphatase [illegible] units. Total cholesterol [illegible] mg%. Ester [illegible]. Total protein 4 [illegible] gm. Albumin 1.4 [illegible] Globulin [illegible] gm. Thymol turbidity 4.7 u. Flocculation [illegible]. Cephalin cholesterol flocculation [illegible]

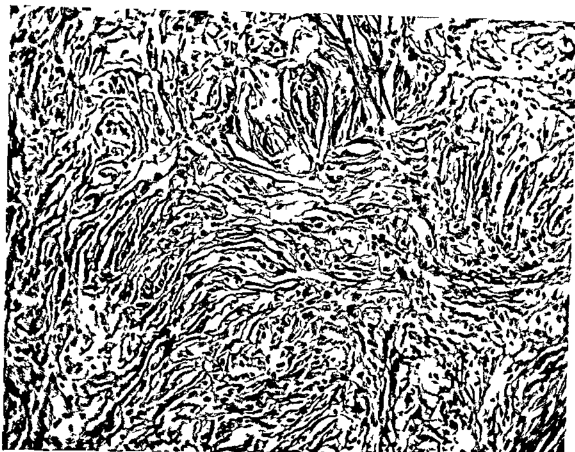


Fig 78 Xanthoma tuberosum Microphotograph (× 00) showing foam cells enmeshed in a fibrous tissue network (Xanthomatous biliary cirrhosis page 455 case 10)

of pulmonary disease Lipid deposits in foam cells were found in the endocardium of the left ventricle by Bevans and Batchelor

Pathology—Summary

A Gross examination
  1 Liver invariably enlarged bile stained granular, and firm
  2 Spleen enlarged
  3 Esophageal varices present
  4 Ascites uncommon
  5 Primary lesion causing posthepatic obstruction usually found

B Microscopic examination
  1 Liver
    a Advanced biliary cirrhosis may be indistinguishable from portal cirrhosis
    b Differential points quantitative (see page 438)
    c Bile lakes commonest in the posthepatic form
    d In instances of intrahepatic obstruction the small bile ducts are obliterated there is intralobular biliary stasis and the larger bile ducts are empty
    e In the case of a posthepatic obstruction the large bile ducts are distended with bile and there is hyperplastic epithelium and marked proliferation of the bile ducts
  2 Xanthoma tuberosum
    a Foam cells are histiocytes filled with lipids chiefly cholesterol
    b Fibrous tissue network
    c Lipids are distributed in small



Fig. [illegible]. A. Biliary cirrhosis (case 10, page 455). Needle biopsy (× [illegible]); special filters were used to bring out the intercellular bile pigment and bile canaliculi plugged with bile thrombi (black). Fibrosis is seen at the bottom of the field.

B. This microphotograph illustrates the intense lymphocytic and mononuclear infiltration (pericholangitis).

droplets that when treated with fat solvents leave a fine mesh work stains yellow or red with Sudan III

d Cholesterol esters produce double refraction of polarized light

3 Spleen

a Fibrosis

b *Congestion*

c Foam cells in xanthomatous typ

4 Arteries

a Atheromatous changes may b marked especially in the pul monary arteries

b Foam cells may be seen in endo cardium

59 Biliary Cirrhosis Clinical and Laboratory Features

Clinical Features

The onset of biliary cirrhosis varies with the location of and the etiologic factor responsible for the obstruction In the fully developed disease the primary and secondary forms may be indistinguishable except in those cases in which a malignant neoplasm intrudes into the clinical picture

A patient with secondary (post hepatic) biliary cirrhosis may give a history of an attack of biliary colic or date the onset of symptoms to the time at which a cholecystectomy or other surgery was performed in the right upper abdominal quadrant The early symptoms may suggest a carcinoma in the area of the common bile duct (pancreas or duodenum) In any case the onset of secondary biliary cirrhosis is usually abrupt and suggests a sudden biliary obstruction It should be emphasized that occasionally a calculous obstruction of the common duct *may be painless and* because of the intermittency or incompleteness of the obstruction may resemble primary biliary cirrhosis

Jaundice and pruritus are the first symptoms of primary biliary cirrhosis They are so constantly present that one should hesitate to make a diagnosis of biliary cirrhosis if they are absent It is interesting that pruritus may precede jaundice This may simply mean that *the patient s perception of itching* was much better than his perception of color it is more than likely that hyperbilirubinemia was present at the time pruritus first appeared This reversal of symptoms also attests to the initial mildness of the jaundice Eventually both symptoms coexist The increase in color of the urine and decrease in color of the stools are noticed along with the jaundice and these like the jaundice may vary in intensity

Abdominal pain is almost always present at least initially and sometimes persists through out the illness in cases of secondary biliary cirrhosis depending on the cause of the ob struction The character and localization of the pain also varies with the lesion causing the obstruction In primary (intrahepatic) biliary cirrhosis pain is usually absent or may be mild If present it consists of an aching or dragging sensation in the right hypochondrium or epigastrium

Chills and fever are present initially if an ascending cholangitis complicates the post hepatic obstruction In primary hepatic di

ease chills and fever denote an intercurrent infection Anorexia is usually slight but the appetite may be excellent throughout the illness in patients with primary biliary cirrhosis In the terminal stage with supervening hepatic failure anorexia may develop Weight loss may occur in spite of adequate food intake and can be explained only on the basis of inadequate absorption Weakness and tiredness are usually late symptoms and are associated with anorexia

Increased frequency of stools is not an infrequent symptom This is not necessarily diarrhea the consistency of the stools may be normal Steatorrhea is responsible for both the increased frequency of stools and the weight loss and is a frequent finding in patients with primary biliary cirrhosis The reduction of bile pigment and bile salt in the intestine may account for the steatorrhea This explanation may not be entirely adequate since frequent stools antedated jaundice and pruritus by seven years in one case (Ahrens et al) Nausea bloating and eructations are rare symptoms and contrary to expectations are not initiated by ingestion of fats

Physical Findings

Jaundice as already noted is among the commonest physical findings it is almost universally present and its intensity varies Scratch marks of the skin may be found as objective evidence of pruritus

Increased pigmentation of the skin is another conspicuous feature and is due to melanin deposition It varies with the duration and intensity of jaundice but this is not so in all series (Ahrens et al) It is most marked in exposed areas of the skin and over the eyelids No mucous membrane pigmentation is associated with this disease Occasionally areas of depigmentation (vitiligo) are found Poor fat absorption has been implicated in the hyperpigmentation

Thickening and dryness of the skin is also observed and may be due to poor absorption of vitamin A Papular and vesicular dermatoses occur in primary biliary cirrhosis Pustular changes may develop from secondary infection These skin lesions are nonspecific in nature and may be related to scratching and infection induced by the pruritus

Xanthomatosis as described under pathogenesis occurs when the biliary obstruction results in a sufficiently high hyperlipemia lipid deposits in the skin known as xanthomas develop These lesions are more likely to occur in the primary than in the secondary disease There are two general types of xanthomas in this disease (1) xanthoma planum and ( )

Table 61

S mm ry   f   p rt d ca es   f gen r lized xanthomatosi   a sociated w th   h on c b lia y ob truct n

	Ag R	F mal	M l	T t l
G o p I				
Confirm d intrah pat c ob tr ct on				
L t r t e (1851 1950)	21 t 6	21	4	5
P e ent ser s	9 to 9	8	0	8
Total		9	4	33
G o p II				
C nfirm d xtr h p t c ob r ct n				
Lit at re (1851 1950)	b rth t 57	17		4
P ee ent series	b rth to 46	1	1	2
Total		18	8	6
G p III				
Ob t ct n of und t m ned r gin				
L t ratu e (1851 1950)	b th to 60	7	16	4
P ent seri s	—	0	0	0
Gr nd Tot l		74	8	10

From F H Ahren Jr and th rs Prim B l a y Cirrhosi Med c ne 29 99 1950



Fig 80 Xanthomatous biliary cirrhosis
A Xantholesma flat yellowish plaques on medial and lateral surface of the eye lids
B Xanthoma planum yellowish linear plaques parallel with creases of fingers
C Xanthoma tuberosum near external malleolus of left foot

xanthoma tuberosum Both lesions have a yellowish orange color The plain xanthomas are more yellow than orange and are distributed chiefly in the flexor creases of the hands el bows and other joints (Fig 80) They are slightly raised soft oval papules When they occur on the eyelids they are known as xanthelasma They start at the inner canthi

and spread outward While xanthelasma are first to develop and are more commonly seen than the other xanthomas they are not of such diagnostic significance since they are found in normo cholesteremic individuals without biliary cirrhosis Xanthalesma may occasionally be the sole expression of the hypercholesterolemia of biliary cirrhosis Jaundice always precedes xanthoma formation The duration of jaundice before the development of xanthomas varies According to Thannhauser this period is about six months although in some patients the jaundice may precede the xanthoma by as long as six years (Ahrens et al) When the patient is seen after xanthomas have developed it may be impossible to determine the chronological relationship between the various signs

The xanthoma tuberosum is the more conspicuous of these lesions (Fig 80c) They consist of round or oval orange yellow soft nontender tumors that vary from the size of a pea to that of a lemon They are most frequently situated on extensor surfaces of joints elbows phalanges ankles and over the Achilles tendons Several adjacent tuberous xanthomas may become confluent and thus form an irregular mass These skin lesions are usually of interest only to the physician and except for the undesirable cosmetic effect are not disturbing to the patient However the tuberous variety especially may become injured because of the exposed areas and infection and all the other symptoms that infection entails may result The xanthoma of the palm may become so extensive that it interferes with flexion of the hands Thannhauser shows a picture of a person so affected in his exhaustive monograph on Lipidoses containing detailed case histories of 21 patients with xanthomatous biliary cirrhosis

Mucous membranes are surprisingly devoid of xanthomas Several small buccal mucous membrane lesions were found in one patient by Ahrens and associates A yellowish discoloration of the fundus is pointed out by Thannhauser but such diffuse discoloration could be due to jaundice Deposition of material in the cornea resembling that seen in xanthomas was reported in one patient with xanthomatous biliary cirrhosis by Gephardt I saw yellowish deposits in the fundi of one woman with xanthelasma chronic jaundice and cirrhosis but she had no other skin xanthoma and the serum cholesterol was only slightly elevated

Spider nevi and palmar erythema are much less frequent in biliary cirrhosis than in portal cirrhosis but they do occur in the advanced stage of the disease Clubbing of the fingers is observed in some patients even when pulmonary or cardiac diseases are absent Weight loss does not occur until late in the course of the disease Evidence of malnutrition and vitamin deficiency is conspicuous by its absence the reverse is true of portal cirrhosis

Liver enlargement is a constant finding in biliary cirrhosis The liver as a rule is larger and more easily palpable than it is in portal cirrhosis The liver frequently extends to the umbilicus and is firm or hard but not nodular There is usually no tenderness but in cholangiolitic cirrhosis following hepatitis tenderness may be elicited on palpation and fist percussion In the secondary (posthepatic) biliary cirrhosis the gallbladder may be palpable as a globular mass below the liver This is suggestive of a malignant obstruction The spleen enlarges later than the liver Occasionally the spleen is barely palpable even though there is marked enlargement of the liver As fibrosis of the liver increases portal hypertension and congestive splenomegaly result The spleen occasionally reaches an enormous size and extends to the iliac crest

Other physical findings are discussed under clinical course

Clinical Features—Summary

A Symptoms

1. **Jaundice**
2. **Pruritus may precede jaundice**
3. **Dark urine**
4. **Light colored stools**
5. **Abdominal pain in the secondary (posthepatic) form depends on nature of primary disease In primary (hepatic) form pain is absent or dragging in nature**
6. **Chills and fever in posthepatic obstruction with cholangitis**

7. Anorexia, slight or absent; develops with hepatic failure
8. Weight loss caused by poor absorption
9. Weakness and tiredness: late symptoms
10. Nausea, bloating and eructations

Physical Findings

A. Skin and appendages
  1. Jaundice of varying intensity
  2. Scratch marks from pruritus
  3. Increased melanin pigmentation, which is most marked in exposed areas, but no mucous membrane pigmentation
  4. Vitiligo
  5. Thickening and dryness
  6. Papular and vesicular dermatoses in the primary type and pustules caused by infection
  7. Xanthomatosis follows jaundice by six months or more
     a. Xanthoma planum in flexor creases of joints and xanthelasma: xanthomas on the eyelid
     b. Xanthoma tuberosum: an orange yellow, round or oval, soft tumor from the size of a pea to that of a lemon on the extensor surfaces of joints
     c. Buccal mucosa occasionally the seat of xanthomas
  8. Spider nevi and palmar erythema are late and infrequent manifestations of biliary cirrhosis
  9. Clubbing of fingers

B. Nutritional deterioration
  a. Weight loss, late
  b. Vitamin deficiency usually absent

C. Liver
  1. Enlarged to umbilicus and is firm or hard and there is tenderness in cholangiolitic type

D. Gallbladder
  1. Palpable in secondary biliary cirrhosis because of malignancy

E. Spleen
  1. Enlarges later than liver
  2. Usually less enlarged than the liver

Clinical Course

In the secondary (posthepatic) type of biliary cirrhosis, the disease may be arrested or a regression may be effected if the obstruction is amenable to surgery. The primary (intrahepatic) biliary cirrhosis usually follows a progressive course.

Signs of advanced disease consist of:

(1) hemorrhagic tendencies
(2) progressive portal hypertension and
(3) Ascites and other manifestations of liver failure

It should be noted that all these signs may be seen as first manifestations of portal cirrhosis but in biliary cirrhosis they develop after years of jaundice. In the cases reported by Ahrens and associates these signs developed a year and a half to 11 years after the onset of the disease.

Hemorrhagic tendencies include bleeding from the gums, epistaxis, ecchymoses and other mucous membrane hemorrhages and may be dependent on hypoprothrombinemia caused by malabsorption of vitamin K as well as defective synthesis of prothrombin. Abnormal capillary fragility and thrombocytopenia are other factors responsible for the hemorrhages (see page 392). Hemorrhage from esophageal varices is the most serious event in the development of portal hypertension. A progressively enlarging spleen forecasts the development of esophageal varices. Bleeding esophageal varices eventually develop in about one fourth of patients with biliary cirrhosis. Ten of 2_ patients in one group showed esophageal varices.

Ascites is a late manifestation of biliary cirrhosis. It is not present as frequently as esophageal varices. Ascites may develop after a massive hemorrhage and resultant depression of the plasma proteins; this took place in one patient whom I observed. Ascites in biliary cirrhosis is not likely to be as massive or as resistant to treatment as ascites in portal cirrhosis (Case 10). Edema frequently accompanies ascites. Distended abdominal veins are not commonly found.

It must be pointed out that the progression of the disease is not continuous; there may be periods during which the signs and symptoms remain stationary and occasionally even re

gress There may be regression in one sphere and progression in another The xanthelasmas in (posthepatic) secondary biliary cirrhosis are known to recede when the obstruction is removed Although Thannhauser contends that xanthomas do not disappear in primary (intrahepatic) biliary cirrhosis Ahrens and co workers present evidence to the contrary This according to Ahrens is dependent entirely on the level of serum lipids I have not seen xanthelasmas or other xanthomas disappear from patients who showed a drop in serum cholesterol

The lack of parallel progression of all the physical and laboratory findings is exemplified by the patients in whom there is a decrease in xanthomas with a decrease in serum lipids while increasing signs of portal hypertension esophageal varices and hemorrhage develop This is actually neither incongruous nor paradoxical since the serum lipid level depends on the degree of biliary obstruction and the ability of the parenchymal cells to synthesize lipids while portal hypertension depends on fibrosis and nodular regeneration (see Laboratory Findings)

Skeletal and dental changes are considered in discussion of roentgenography (p 451)

Clinical Course—Summary

A The course of biliary cirrhosis

1 May be arrested in posthepatic biliary cirrhosis

2 Progressive in the primary (hepatic) type

3 Signs of advanced disease

a Hemorrhages

b Portal hypertension

c Ascites (occurs usually after years of jaundice)

4 Esophageal varices develop in one fourth of patients

5 Ascites not as common may follow hemorrhage from varices

6 Edema may follow ascites

7 Xanthelasmas may decrease or disappear in spite of progression of the disease

Laboratory Findings

The laboratory findings in biliary cirrhosis are dominated by the results of impaired bile flow hyperbilirubinemia and hyperlipemia Hyperbilirubinemia is almost always present in biliary cirrhosis and is usually very high The constancy and height of the serum bilirubin as well as its persistence for years without impairing the general health of the patients are at variance with the situation in portal cirrhosis The total serum bilirubin may be very high One patient with xanthomatous biliary cirrhosis had a serum bilirubin of 50 mg % (see table 62) and another one with biliary cirrhosis without xanthomatosis had a serum bilirubin of 60 mg % One of the patients reported by Ahrens and co workers had a serum bilirubin of 34 8 mg In the primary (intrahepatic) disease the serum bilirubin varies widely and reaches its height even when the obstruction is not complete Occasionally a patient may have a normal serum bilirubin The prompt direct reacting bilirubin is elevated and thereby confirms the regurgitant nature of the hyperbilirubinemia

TABLE 62

Labo ato y fi d gs in a mal w th xanthom to b l ry c rrh

Xanthomato s b liary cirrh is (FCW)

Date	Total Protein	Alb	Globulin α	Globulin β	Globulin γ	Phosphatase	Serum Bil	Cholesterol Total	Cholesterol Free %	C-C F	Thymol Turb	Thymol Floc
1 3	9 1	3 0	1 3	1 55	3 25	40	26 0	451	13	4+	17 6	3+
2 1	8 7	2 5	1 7	1 55	2 95	82	8 5	98	22	3+	19 4	1+
2-24	8 8	6	1 5	1 75	2 9o	87	50 0	312	17	0	19 4	1+
3	6 9	1 9	1 5	1 35	15	9	9 2	4	10	0	15 6	0
3-24	6 7	1 8	1 4	1 3	15	100+	11 6	177	36	0	9	3+
4 7	8 4	4	1 7	1 3	3 0	76	14 6	416	9	0	10	0

F m Spellberg d co-w rkers C troenterology 14 11 1950

Hypercholesterolemia is one of the most interesting and puzzling as well as one of the leading diagnostic laboratory findings in biliary cirrhosis. The height of the total cholesterol and total lipid determines the development of xanthomas. The cause of the hypercholesterolemia is threefold:

1. Retention of cholesterol because of biliary obstruction.
2. Increased production of cholesterol.
3. Decreased destruction of cholesterol by liver cells.

That biliary obstruction is not the sole agent responsible for hypercholesterolemia is evidenced by the fact that in the complete biliary obstruction of the posthepatic type hypercholesterolemia does not reach the fantastic height that it does in cases in which the intrahepatic obstruction is incomplete. The rise in serum bilirubin parallels the severity and degree of biliary obstruction, but hypercholesterolemia does not parallel hyperbilirubinemia. In one of the patients I observed, the total cholesterol was 616 mg with a serum bilirubin of 16.5 mg, while six weeks later the serum bilirubin had nearly doubled to 30 mg but the cholesterol had decreased by nearly half to 31[illegible] mg (table 62) (FCW). In another patient (M M) (table 63) the serum cholesterol was 716 mg and the serum bilirubin 4.4; one month later the cholesterol dropped to 576 mg while the bilirubin rose to 6.4 mg. If these two patients are compared, the discrepancy between the serum bilirubin, which is a sign of obstruction, and the serum cholesterol is even more marked and emphasizes that the height of serum cholesterol does not depend solely on biliary obstruction.

There is ample evidence that the liver synthesizes cholesterol and that the height of the blood cholesterol level is at least in part dependent on liver synthesis even in a normal person. There is also evidence that in biliary cirrhosis the cholesterol is endogenous and not exogenous. This endogenous increment of cholesterol is due to increased synthesis by the liver cells, a process that is peculiar to this form of liver dysfunction. It can be compared to the hyperfunction of other organs after mild damage. As the liver damage becomes more marked, the cholesterol drops. When liver failure supervenes, hypocholesterolemic levels may be reached. For this reason, when liver failure develops slowly, the blood lipids may decrease and remain decreased for a sufficiently long period of time to result in disappearance of xanthomas while the patient gradually succumbs to liver failure.

The total cholesterol may reach a level as high as 1 500 mg per 100 cc, but usually lower values are recorded. The cholesterol esters in my experience and in the experience of others (Ahrens et al), are decreased so that the normal ratio between free and esterified cholesterol is disturbed. Thannhauser reports that most of his cases show a greater amount of the cholesterol in the esterified form. In my two patients the cholesterol esters were about 20 to 25 % of the total cholesterol. This amount is confirmed by Ahrens' observations. Since the total cholesterol value is markedly increased, the absolute value of the cholesterol esters remains at a nearly normal level. This is in keeping with the experimental observations of ligation of the common duct in animals. When liver failure supervenes, the fall in cholesterol esters precedes the fall in free cholesterol. The cholesterol esters may eventually disappear completely.

The increase of total lipids parallels the rise of the serum cholesterol. The normal value of 475 to 7[illegible]5 mg per 100 cc is quadrupled. One of my patients showed a total lipid value of 2 689 mg and the other 2 095 mg. The total lipids may exceed 3 000 mg per 100 cc. In spite of the marked hyperlipemia, the serum is clear and not opalescent as it is in other types of hyperlipemias. This is due to the fact that lipid increase is the result of cholesterol and phospholipid elevation while the neutral fats remain at the usual level. Phospholipids and cholesterol are loosely bound to globulin molecules and are therefore in colloidal suspension. The phospholipid is therefore another lipid fraction markedly elevated in biliary cirrhosis; the lecithin fraction makes up about 80 %, sphingomyelins less than 10 %, and cephalin the rest. The phospholipids comprise more than half of the total lipids and usually exceed cholesterol in quantity.

Lecithin, like cholesterol, is synthesized in the liver and excreted in the bile. The mecha

nism of serum elevation is similar to that discussed for cholesterol. Hyperlecithinemia is even more remarkable than hypercholesterolemia because this lipid fraction is not ordinarily disturbed in other forms of liver disease; therefore its elevation must depend on a disturbance of the liver cells that is peculiar to this disease. An unusual amount of choline is required and utilized for synthesis of lecithin. In biliary cirrhosis a lipotropic substance aids the disturbed lipid metabolism.

Serum alkaline phosphatase elevation is another characteristic laboratory finding pointing to biliary obstruction. This enzyme reaches very high levels that are frequently out of proportion to the bilirubin level and in spite of incomplete biliary obstruction. One patient showed over 100 Huggins units of alkaline phosphatase when the bilirubin level was 11 6 mg, and 40 units of phosphatase when the serum bilirubin level was 26 mg (table 62). Another patient (M. M.) had an alkaline phosphatase level of 91 8 and a bilirubin level of 6 4 (table 63). Observation of these findings leads to the conclusion that biliary obstruction is not the sole causative factor in alkaline phosphatase elevation. The disproportionate rise of the alkaline phosphatase level as compared with the serum bilirubin level in primary biliary cirrhosis is a distinctive feature and may help to distinguish this type of jaundice from simple posthepatic jaundice.

The alkaline phosphatase elevation is not directly proportionate to hypercholesterolemia and these two values may vary independently of each other. In one of our patients after a severe hemorrhage from esophageal varices the serum bilirubin and cholesterol levels dropped but the alkaline phosphatase level rose slightly. This enzyme like cholesterol drops in instances of hepatocellular failure and may reach normal level prior to death from liver failure.

Marked hyperbilirubinemia, hypercholesterolemia (hyperlipemia) and hyperphosphatasemia are the distinctive laboratory findings in biliary cirrhosis. They point chiefly to interference with bile flow and distinctive alteration of liver cell function. It should be remembered that the laboratory features of primary (hepatic) biliary cirrhosis are similar to those seen in posthepatic jaundice. Alterations of other laboratory tests pointing to hepatocellular damage are also present but may occur late in the disease.

Serum protein alterations are frequent in this disease and show some distinctive features. The total protein may be normal or even high. The serum albumin is depressed and the globulins are markedly elevated, especially the gamma globulin. The globulins make up a large proportion of the total proteins. By using the NaCl-NH_4Cl fractionation technique it was found that our patient (M. M.) had three times as much globulin as albumin (table 63): the total protein was 7 9 gm, albumin 1 9 gm and globulin 6 gm. The gamma globulin value alone was 3 1 gm per 100 cc, more than that of the albumin. The other patient (table 62) likewise showed a serum globulin value of 6 gm per 100 cc or above. The alpha and beta globulins were also elevated but not to the extent that the gamma fraction was. The elevation of the alpha and beta globulins is to be expected since they form the lipoproteins and these hyperlipemic persons require more of these proteins to transport the lipids.

Electrophoretic fractionations of the serum

TABLE 63

Xanthomatous Biliary Cirrhosis (Female M. M.) Liver Function Tests and Serum Lipids

Date	Serum Bilirubin Mg %	Alkaline Phosphatase (units)	Cholesterol Total Mg %	Cholesterol Ester (%)	Total Protein Gm %	Albumin Gm %	Globulin α	Globulin β	Globulin γ	Cephalin Cholesterol Flocculation	Total Lipid gm %	Phospholipid (mg %)	Thymol Turbidity (units)	Thymol Flocculation
16-50	5 4	70	832	8	6	2	0	0 85	55	3+			47 2	4+
50	4 4	60 3	716	11	7 1	2 3	1 9	0 9	2 0	1+			31 8	3+
3-4-50	6	37 0	59	9 5	7 7	1 8	2 1	1 5	55	0	689	1 5 4	17	+
3-18-50	6 4	91 8	5 6	60	7 9	1 9	0	0 9	3 1	0		1 16	0 0	3+

TABLE 64
Electrophoretic Fractionation of Plasma Proteins in a Patient with Xanthomatous Biliary Cirrhosis
As Percent of Total Protein

Date	Albumin	Alpha Globulin	Alpha Globulin	Beta Globulin	Fibrinogen	Gamma Globulin
10/13/49	-4 15	5 5	8 50	17 07	14 97	9 78
10/31/49	4 96	5 34	8 45	16 83	13 95	30 46
1/19/50	33	6 13	7 19	17 19	15 37	31 19
5/13/50	5 53	6 17	13 49	6 69	16 74	31 39

proteins in one patient (F C W) confirmed the results of chemical protein fractionation The albumin varied between 22 and 25% while the gamma globulin varied between 30 and 31 5% of the total protein The gamma globulin value was likewise elevated The alpha globulin value was nearly 20% of the total protein on one occasion (table 64) Fibrinogen was slightly elevated

Results of flocculation tests become abnormal and there is alteration of the serum proteins Thymol turbidity is usually more strongly and consistently positive than other flocculation tests In our patients the thymol turbidity was in the neighborhood of 20 units The experience of others is in keeping with this Hyperlipemia undoubtedly influences the production of this strongly positive reaction The findings of the thymol flocculation are not as consistently positive as those of the thymol turbidity test The zinc sulfate turbidity is likewise strongly positive Results of the cephalin cholesterol flocculation test are neither as strongly nor as consistently positive as those of the other tests mentioned and they may be negative even though there is a strongly positive thymol turbidity (see tables 62–63)

The serum prothrombin is either normal or only slightly depressed Slight hypoprothrombinemia usually responds to vitamin K and is probably due to defective absorption because of the deficiency of bile in the intestines however in the terminal phases of biliary cirrhosis hypoprothrombinemia may become severe and fail to respond to vitamin K because it is dependent on defective hepatocellular function Serum cholinesterase activity is usually reduced and serum vitamin A levels are depressed

A bromsulphalein excretion test is usually not done in instances of biliary cirrhosis because of persistent jaundice Ahrens and associates however performed this test in their patients and found a bromsulfalein retention between 15 and 39% after 45 minutes Because nearly all of these patients were jaundiced most of the bromsulfalein retention can be accounted for on the basis of obstruction to bile flow and the parenchymal cell defect in excreting this dye can be adjudged minor in nature Bromsulfalein retention is much greater in portal cirrhosis if the accessory effect of the obstructive element is taken into consideration Thannhauser reports much greater bromsulfalein retention as high as 80%

The stools almost always contain urobilinogen in primary (intrahepatic) biliary cirrhosis Absence of urobilinogen in the stools continues only for a brief period of time and there is wide variation in the quantity of urobilinogen from day to day as judged by the color of the stool or its chemical estimation There is always a reduction in the quantity of urobilinogen in the stools except in the rare anicteric form The fat content of the stools is also increased in many patients Occult blood may be found in the presence of gastrointestinal bleeding Occasional decrease in pancreatic trypsin and lipase secretion has been noted by Ahrens and associates

A hemogram shows no characteristic changes Leukopenia seen in portal cirrhosis with splenomegaly is rare in biliary cirrhosis One of our patients showed on one occasion 3 600 leukocytes per cubic millimeter of blood The white blood cell count is usually normal but occasional marked leukocytosis has been observed as has eosinophilia (Ahrens et al) The thrombocytes may occasionally be decreased The thrombocyte count dropped to 112 000 per cubic millimeter in one patient (Case 10 p 455) A mild normocytic normo-

chromic anemia is frequently observed During a severe esophageal hemorrhage anemia may become grave

Roentgenography is of help in the diagnosis of esophageal varices One patient had large esophageal varices demonstrated by a roentgenogram (see fig 81) The search for esophageal varices should be supplemented by esophagoscopy Osteoporosis is another frequent finding in patients with biliary cirrhosis and may lead to spontaneous pathological fractures I have seen compression fractures of a lumbar vertebra and two ribs without trauma in a patient with biliary cirrhosis Skeletal pain should initiate a search for fractures The pathogenesis of osteoporosis may be twofold (1) there may be a lack of calcium and vitamin D due to intestinal malabsorption (steatorrhea) and (2) hypoestrogenism may lead to poor bone formation Dental caries and thinning of the peridental membranes may be very marked and may be an expression of disturbed calcium metabolism These disturbances may be accompanied by marked bleeding from gums even in the absence of disturbed clotting mechanism Abnormal small bowel patterns have been ascribed to excessive amounts of fat in the intestines however unless special precautions are taken in the selection of the medium and the interpretation of small bowel films (Kirsch and Spellberg) minor alterations of the small bowel pattern cannot be relied on too much Cholangiograms are of inestimable value in eliminating posthepatic obstruction in some problem cases



Fig 81 Roentgenogram of esophagus showing large [illegible] patient with xanthomatous biliary [illegible] (Same patient as Fig [illegible] 8 9 80 [illegible] Table 8 [illegible] 84)

An elevated basal metabolic rate is frequently found in patients with biliary cirrhosis The elevation occurs with a normal iodine uptake and indicates the absence of thyroid dysfunction Increased oxygen consumption may be due to the increased bulk of the liver Urinary 17 ketosteroid excretion is reduced in some patients but this is not as common as it is in portal cirrhosis Eosinophil response to adrenalin and adrenocorticotropic hormone is usually normal and indicates intact pituitary and adrenal response

Flat glucose tolerance curves when glucose is administered either orally or intravenously and poor response of the blood sugar to administration of epinephrine has been reported by McCabe and Thompson The former has been interpreted as a result of increased glucose utilization and the latter as caused by defective glycogen breakdown or lack of glycogen storage An abnormal response to a galactose tolerance test may also be noted

Laboratory Findings—Summary

I Depending on bile flow impairment
 A Hyperbilirubinemia fluctuates, but may reach 60 mg per 100 cc
 B Hyperlipemia up to 3 000 mg % or more
  1 Serum is clear not turbid due to
   a Hypercholesterolemia as high as 1 500 mg %
   b Hyperphospholipidemia may equal or exceed the cholesterol level
    (1) Lecithin 80%
    (2) Sphingomyelin 10%
    (3) Cephalin the remainder
 C Alkaline phosphatase elevation may reach fantastic heights

(A–C: Distinctive features of biliary cirrhosis and simulate posthepatic jaundice)

II Depending on hepatocellular changes
 A Serum proteins
  1 Total — normal or elevated
   a Albumin is depressed late in disease
   b Globulins total elevated to 6 gm %
    (1) Gamma markedly elevated to 3 gm % or above
    (2) alpha and beta also elevated carriers of lipids
 B Flocculation tests show
  1 Thymol turbidity markedly positive due to inflammatory parenchymal reaction and hyperlipemia
  2 Thymol flocculation not so positive
  3 Zinc sulfate turbidity markedly positive
  4 Cephalin cholesterol flocculation not consistently positive
 C Serum prothrombin
  1 Decreased early because of faulty absorption of vitamin K
  2 Decreased late because of hepatocellular failure does not re-spond to vitamin K
 D *Serum* cholinesterase activity an- vitamin A levels depressed
 E Bromsulphalein tests are usuall- not done
  1 *Retention is at least in part du- to obstruction*

III Other tests
 A Stools
  1 Urobilinogen, always present in hepatic form of disease but al- ways reduced and fluctuating
  2 Fat content increased
  3 Occult blood may be present
 B *Intestinal* pancreatic enzymes may be decreased
 C Hemogram
  1 Leukocytes, usually normal
  2 Leukopenia and leukocytosis oc- casionally present
  3 Normochromic, normocytic ane- mia
  4 Thrombocytopenia occasionally present
 D Roentgenography
  1 Esophageal varices
  2 Osteoporosis may result in pathological fractures
  3 Abnormal small bowel pattern
  4 Cholangiography of value in eliminating the possibility of a post hepatic obstruction
 E Endocrine tests
  1 Basal metabolic rate elevated but iodine uptake normal
  2 Urinary 17 ketosteroid excretion reduced in some patients
  3 Eosinophil response to adrenalin and ACTH is normal
  4 Curves of glucose tolerance tests glucose administered both orally and intravenously are flat increased utilization?
   a Poor rise of blood sugar when epinephrine administered indicates defective glycogen breakdown
  5 Galactose tolerance abnormal

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Biliary Cirrhosis Treatment, Prognosis, and Differential Diagnosis

Treatment

Treatment of biliary cirrhosis should be directed toward the following objectives
(1) removing biliary obstruction
(2) combatting infection
(3) treating liver failure and its concomitants and
(4) reversing abnormal lipid metabolism

Removal of biliary obstruction can be effectively achieved only if the obstruction is posthepatic. Clinically this location is suggested by the pain of biliary colic with typical localization and radiation preceding dyspepsia and chills and fever suggesting cholangitis. If the clinical picture is compatible with posthepatic obstruction laparotomy with cholangiography should be considered. Needle liver biopsy may help preoperative differentiation. The presence of bile necrosis (bile lakes) dilated large calibre biliary radicals and marked bile duct reduplication attest to posthepatic obstruction however because of the difficulty in differentiating between primary and secondary biliary cirrhosis on the basis of hepatic histology alone this approach may be doomed to uncertainty and equivocation. *If unequivocal clinical laboratory and histological* evidence of marked liver failure are absent jaundice of more than three months duration should be subjected to exploration and cholangiography with the hope of finding and removing the obstruction or shortcircuiting the *bile passages*

While the cause in most cases of primary (intrahepatic) biliary cirrhosis is obscure it is likely that infection plays a role. Bacterial intrahepatic cholangitis may be the initial episode in some patients. Rachmilewitz recently reported five cases of chronic intrahepatic cholangitis that responded to ? gm of sulfadiazine daily. These patients had hepatomegaly splenomegaly jaundice and recurrent attacks of fever. Such treatment may forestall the development of chronic biliary cirrhosis. It is advisable to use a less toxic antibiotic such as aureomycin or terramycin in doses of one to two grams a day orally. Large doses of these drugs may also subject the individual to liver injury (p 177). Intubation of the second portion of the duodenum and culture of the contents may suggest the organism responsible.

Treatment of hepatocellular failure and its concomitants such as ascites and esophageal varices is the same as that of portal cirrhosis (pp 579 355). It consists of dietary measures rest attention to esophageal varices and the treatment of ascites.

Xanthomatosis and hypercholesterolemia have intrigued therapists ever since these phenomena were observed. As has been pointed out xanthomatosis may decrease or even disappear if the hypercholesterolemia is abolished. Treatment directed toward the resorption of xanthomas was especially logical when xanthomatosis of the intrahepatic bile ducts was considered to be the primary cause of the biliary obstruction. Now that it is generally *conceded that hypercholesterolemia and xanthomatosis* are secondary phenomena it seems illogical to direct so much attention to disturbed lipid metabolism. Thannhauser still advises the unpalatable purely vegetarian diet devoid of animal fat and hence exogenous cholesterol. Since the liver is capable of synthesizing cholesterol it is easy to see the reasons for which this diet fails even in this objective. It has been my experience as well as that of others that this diet is not effective. The unpalatability of the diet may result in anorexia and in inadequate intake of proteins and carbohydrates as well. The cholesterol drops spontaneously with progressive liver damage

This happens without a cholesterol free diet as was noted in one of our patients (see page 455) however it does seem reasonable to reduce the amount of animal fat in the diet to a level which does not interfere too much with the patient's general nutrition

Various lipotropic agents have been recommended for the hyperlipemia among these are choline methionine and inositol Since these patients do not have a fatty liver and on the contrary do have an abundance of choline to synthesize lecithin these remedies seem illogical I have not found them of value There are however some reports in the literature that suggest the effectiveness of these agents Gephardt reported a drop in the total lipids and phospholipids in one patient with xanthomatous biliary cirrhosis who was fed a low fat diet (carbohydrate 302 gm protein 89 gm fat 27 gm supplemented with 1 5 gm of choline and 3 gm of inositol) A rice diet which is low in salt and fats was used by McCabe and Thompson and it lowered the serum lipids but while on this diet which is also deficient in protein the patient developed ascites

Various hormones have been tried in therapeutic amounts in primary (intrahepatic) biliary cirrhosis The use of such substances has a rational basis in view of the marked predilection of this disease in women but as happens frequently attractive theories are upset by cold facts Diethylstilbestrol administered orally to two patients resulted in increased lipemia due especially to increased phospholipids and neutral fats and resulted in lipemic serum Methyltestosterone produced a fall in the serum lipids and improvement of pruritus but the bilirubin rose indicating increased biliary obstruction (Ahrens et al) According to Ahrens and associates adrenocorticotropic hormone had a deleterious effect it produced a rise in serum bilirubin and the development of ascites McCabe and Thompson reported a slight decrease in serum lipids after therapy with 100 mg of cortisone administered daily for six days They found increased cholesterol esters but decreased total cholesterol as well as the other lipid components These changes however, are so slight that they suggest spontaneous variations

It cannot be emphasized too much especially for those who are in search of therapeutic agents for this disease that spontaneous improvement of the clinical state and decrease of hyperbilirubinemia and hyperlipemia occur This improvement may proceed to the point of almost complete disappearance of jaundice and decrease of xanthomatosis The cause for these spontaneous changes is shrouded in the same mystery as the etiology of the primary disease and the pathogenesis of the metabolic disturbances There is to date no single or group of therapeutic agents that can be relied on to produce a reversal or arrest the inexorable development of the disease General supportive measures and the general therapeutic approach outlined for portal cirrhosis offer the best hope of prolonging the life and increasing the comfort of the patient

Treatment of Complications

Osteoporosis may produce a good deal of pain discomfort and disability Vitamin D in doses of 2 000 units a day with assurance of good calcium intake is very helpful if the condition is not too far advanced Because of the susceptibility to fractures undue exertion and even slight trauma should be avoided If fractures develop they should be treated in the usual manner The marked dental caries and gingival disease should receive frequent dental attention

General atherosclerosis and coronary atherosclerosis consequent to the hypercholesterolemia bring to mind the need to watch for and to treat cardiovascular complications arising from them Patients with the most extensive cutaneous xanthomatosis show less atheromatosis than those lacking or with minimal xanthomatosis The deposition of lipids in various sites may depend on the relative concentration of the various lipids as well as on local factors It also is a curious fact that in spite of the lipid disturbance and predisposition to atheromatosis these patients rarely die from the various cardiovascular complications

Treatment—Summary

I Removal of posthepatic obstruction
   A Clinical picture evaluated with obstruction in mind
   B Needle liver biopsy for differentiation
   C Laparotomy and cholangiography to determine site of obstruction
II Eradication of infection
   A If cholangitis exists antibiotics and chemotherapy
      1 Terramycin } no more than
      2 Aureomycin } 2 gm daily
      3 Sulfadiazine with caution
      4 Other antibiotics when indicated
III Treatment of hepatocellular failure and complications
IV Treatment directed toward hypercholesterolemia and xanthomatosis
   A Vegetarian low cholesterol diet of no value
   B Lipotropic agents
      1 Choline } of doubtful value
      2 Methionine } of doubtful value
      3 Inositol } of doubtful value
   C Hormones
      1 Diethylstilbestrol } none of these are of proven value
      2 Methyltestosterone
      3 Adrenocorticotropic hormone
      4 Cortisone
V Treatment of complications
   A Osteoporosis
      1 Vitamin D 2 000 units daily
      2 Adequate calcium intake
      3 Avoid strain and trauma
      4 Detect fractures and treat them early
   B Dental caries and gingival disease
      1 Should be detected and treated early
   C Atherosclerosis
      1 Watch for cardiovascular complications and
      2 Treat them as they arise

Prognosis

Except in cases of occasional secondary biliary cirrhosis resulting from a remediable posthepatic obstruction the prognosis is poor The disease advances in spite of all therapeutic efforts and terminates fatally within about seven years after the onset This means that the entire duration of the disease may even be shorter than in portal cirrhosis since the onset in biliary cirrhosis can be determined accurately by the onset of jaundice or pruritus while in portal cirrhosis the onset is insidious and conjectural Death may occur as early as 2 years after the onset but patients are known to live as long as 11 years (table 65) One of our patients died 6 years after the onset of illness

Cause of Death

The cause of death is similar to that in portal cirrhosis The chief factors are (1) hepatic failure (2) hemorrhage and (3) infection in that order of frequency (table 65) Hepatic coma may develop and remit numerous times before the patient dies While the same is also seen in portal cirrhosis it is more likely to occur in biliary cirrhosis it did in our patient (case 10) It may be a sign that sufficient functioning hepatic tissue is present to allow partial recovery Hemorrhage from esophageal varices may cause death by exsanguination or by precipitation of hepatic failure Of the infections pneumonia is the one most likely to cause death

The following case report demonstrates some of the salient clinical laboratory and pathological features of xanthomatous biliary cirrhosis and the discouraging results of therapy and the relentless downhill course

Case 10

This male patient was first seen in November 1948 at the age of 4[illegible] His chief complaints were jaundice pruritus and anorexia He dated his illness to 1944 when while in the army discoloration of his skin was noted His disability at the onset was relatively mild and he was not discharged because of it but given lighter duties He was discharged in 1945 because of age rather than illness Anorexia resulted in a weight loss of 30 pounds over a period of four years weakness and fatiguability supervened The icterus became progressively severer His only other symptom was occa

TABLE 65

Prognosis, Complications, and Cause of Death in Patients with Xanthomatous Biliary Cirrhosis

Authors	Duration	Xanthomas	Ascites	Esophageal Varices	Gastrointestinal Hemorrhage	Cause of Death
Robertson and Carter 1952	6 yr 4 mo (D)	+	+	+	+	Hepatic coma
Bevans and Batchelor 1950	7 yr + (D)	+	+	o	o	Hepatic coma?
Eusterman and Hamilton 1944	[illegible] yr (D)	+	o	+	+	Hepatic coma
McCabe and Thompson 195		+	+	o	o	Living
Ahrens et al 1950	to 7 yr (D) (6 patients)		6/22*	10/	4/17	Liver failure 5/20
	2 to 11 yr (L) (11 patients)	+				
MacMahon and Thannhauser	6 yr (D)		o	o	o	Pneumonia
	6 yr (D)	+	o	+	+	Hemorrhage
	5 yr (D)			?	+	Hemorrhage
	5 yr (L)				+	Living
Spellberg	6 yr (D)	+	+	+	+	Hepatic failure

D = Patient deceased
L = Patient living
+ Present
o Absent

* Numerator = number of patients in the particular category
Denominator = total number of patients in series

sional drowsiness but on questioning increased color of the urine was admitted No mention of abdominal pain clay colored stools diarrhea or melena was elicited in the history

The outstanding features on physical examination included the marked icterus of the skin and mucous membranes and the xanthomatose These were of all three varieties xanthelasma of both lower and upper eyelids (Fig 80) xanthoma planum especially of the flexor surfaces of the hands and creases of the fingers and a large xanthoma tuberosum of the medial malleolus of the left ankle and a smaller one on the extensor surface of the right elbow The patient was not certain of the time of origin of these deposits but thought they started prior to 1937 that is the icterus antedated the xanthomas by several years Several yellowish pinhead sized deposits were seen in both fundi which suggested the possibility of cholesterol deposit in the retinas

The other findings that pointed to liver disease were several small spider telangiectasias over the manubrium sterni hepatomegaly, and splenomegaly Both the liver and spleen were firm nontender and extended about four fingerbreadths below the corresponding costal margins No superficial dilated venous channels were noted on admission nor was ascites There was no peripheral edema The blood pressure was 110/80 mm Hg and other aspects of the cardiovascular system were normal except for a soft systolic murmur at the apex of the heart

Laboratory data confirmed the clinical impression of xanthomatous biliary cirrhosis On admission there was a slight anemia with 3 700 000 erythrocytes, 11 5 gm of hemoglobin, and 6 000 leukocytes

The results of the liver function tests varied as may be noted from Table 62 but shortly after admission the patient s serum bilirubin was 16 5 mg per 100 cc , total protein 8 7 gm with 2 7 gm of albumin and 2 85 gm of gamma globulin 1 85 gm of beta globulin and 1 3 gm of alpha globulin The total lipids were [illegible]095 mg cholesterol 616 mg with [illegible]1 % esters and 787 5 mg of phospholipids and the serum was not lipemic It will be noted from the Table that the thymol turbidity was unusually high over 20 units while the thymol flocculation

was at times only 1+ and the cephalin cholesterol varied between 0 and 4+ Two hour urobilinogen excretion varied between 0 05 mg and 0 45 mg per 100 cc Stools were positive for urobilinogen Prothrombin time was normal (13 seconds)

The nonprotein nitrogen was 37 mg except shortly after the hemorrhage when it rose to 60 mg per 100 cc Uric acid was 3 5 A glucose tolerance test glucose administered orally showed a normal curve Serum calcium was 9 1 mg and phosphorous 3 3 mg per 100 cc Gastrointestinal series showed extensive esophageal varices (Fig 81) Chest film showed calcification of the aortic arch An electrocardiogram was normal

The patient s course in the hospital was marked by a massive upper gastrointestinal hemorrhage from an esophageal varix in February 1949 three months after admission It should be noted that there was a marked drop of the serum protein (table 6) that was followed by ascite which required a paracenthesis With replacement of the blood and the return of the proteins to the prehemorrhage level the ascites subsided and did not require further paracenthesis There was also a marked drop in the serum cholesterol and there were transient episodes of stupor that suggested hepatic coma The erythrocyte count at that time dropped to a low point of 1 840 000 When this rose to over 3 700 000 with blood transfusions the cerebral symptoms disappeared The thrombocytes remained over 200 000

In spite of a low cholesterol diet supplemented with vitamin B complex inositol methionine and choline the patient s course continued downhill In 1950 ascites returned and peripheral edema developed both of which were treated with low sodium intake and mercurial diuretics In January 1950 pain developed in the right side of the chest and proved to be due to spontaneous fracture of the seventh and eighth ribs during the next month a pathological fracture of the first lumbar vertebra was detected

The deterioration of the patient s clinical state continued and there were recurrent episodes of stupor It should be noted that the patient was cured of the hypercholesterolemia which decreased to 157 mg per 100 cc with 12% esters but the serum bilirubin increased to 41 mg The alkaline phosphatase remained high 50 Bodansky units On May 6 1950 the patient was given 20 mg of adrenocorticotropic hormone every eight hours In spite of an apparent increase in appetite coma developed six days later and the patient expired after a convulsion that occurred seven days after the institution of therapy with ACTH and approximately six years after the onset of the disease

Needle liver biopsy and biopsy of cutaneous xanthomas (Fig 78 and 79) showed typical changes of xanthomatous biliary cirrhosis

Diagnosis and Differential Diagnosis—Summary

I Diagnosis of primary hepatic biliary cirrhosis depends on

A Clinical evidence

1 Patient usually a middle aged woman

2 Jaundice of long duration and progressive or of varying intensity accompanied by

a Pruritus

3 General state of patient good

4 Liver large and firm

5 Spleen moderately enlarged

6 No ascites

B Laboratory findings

1 Hyperbilirubinemia moderate to marked

2 Urobilinogen in stools present but reduced

3 Alkaline phosphatase markedly elevated

4 Hyperlipemia with clear serum due to hypercholesterolemia and hyperphospholipidemia

5 Total protein normal or high gamma and beta globulin

6 Liver biopsy shows pericholangiolitis bile stasis periportal and perilobular fibrosis

II Secondary (posthepatic) biliary cirrhosis differs from primary biliary cirrhosis by

A Clinical differences

TABLE 65

Prognos s Comp cat ons and Cause of Death in Pa ents w th Xanthoma ous B l a y C ho s

A ho	D n	Xa ho-m	A	E phag al	G o-na Hem hag	C f Death
Robertson and Carter 1952	6 yr 4 mo (D)	+	+	+	+	H pa c coma
Bevans and Batchelor 950	7 yr + (D)	+	+	o	o	Hepa coma?
Eusterman and Ham l on 1944	3 yr (D)	+	o	+	+	Hepa c coma
McCabe and Thomp on 1952		+	+	o	o	L v ng
Ahrens et al 1950	2 to 7 yr (D) (6 pa t ents)		6/22*	10/ 2	4/ 7	Li e fa ure c 20
	to 1 yr (L) (11 pa t en s)	+				
MacMahon and Thann hauser	6 yr (D		o	o	o	Pn umon a
	6 yr (D)	+	o	+	+	Hemo h g
	5 yr (D)			?	+	Hemorrhage
	5 yr (L)				+	Liv ng
Spellbe g	6 yr (D)	+	+	+	+	H pa fa ur

D = Pa ent decea ed
L = Pat ent l v ng
+ Present
o Absent

Nume a o = n mber of pat en s n the par cula catego y
Denom na or = o al number of pat ents n e es

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  - **5 Spleen moderately enlarged**
  - **6 No ascites**
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II Secondary (posthepatic) biliary cirrhosis differs from primary biliary cirrhosis by
- **A Clinical differences**

1. Onset
   a. With colicky pain, chills, and fever
   b. After biliary surgery
   c. Associated with signs of a *malignant neoplasm*
2. Jaundice progressive without remissions
3. *Stools acholic*

B. Laboratory findings
1. *Hyperbilirubinemia progressive*
2. *Stool urobilinogen absent*
3. Hyperlipemia less marked
4. Serum protein alterations less marked
5. Cholangiogram necessary to demonstrate posthepatic block
6. *Liver biopsy shows*
   a. *Inflammatory* changes around and distention of larger bile ducts
   b. Marked bile duct prolifera tion
   c. Bile necrosis

III. *Xanthomatous* form of biliary cirrhosis commoner in intrahepatic than in posthepatic type diagnosed by the presence of

A. Cutaneous xanthomas
1. Xanthelasma of eyelids
2. Xanthoma planum of the flexor creases of joints especially *the hands*
3. Xanthoma tuberosa over extensor *surfaces especially over* Achilles tendon

B. Marked hyperlipemia
1. *Usually over* 1 800 *mg* per 100 cc of blood
2. Very high serum cholesterol and phospholipids

The differentiation between biliary and portal cirrhosis is more of academic than practical importance moreover this differentiation may be impossible not only clinically but at times even pathologically The differential features can best be presented in table form, Table 66

The *differential diagnosis of biliary cirrhosis* includes all conditions that may be accompanied by jaundice The *differential* diagnosis of jaundice has been discussed in detail in *Section III* The significant features of biliary cirrhosis are *that it has most of the features* of posthepatic jaundice on which a e *super imposed* some of the features of hepatic

TABLE 66

Differential Diagnosis of Biliary and Portal Cirrhosis

Clinical Aspects	*Biliary Cirrhosis*	*Portal Cirrhosis*
Age	Any age usually younger persons	40 to 60 yr
Sex	Woman	Man
Alcoholism	*Rare*	*About 50%*
Malnutrition	*Rare*	*Frequent*
Jaundice	Almost always present marked early	*Uncommon* mild late
Xanthomas	*Present at times*	*Absent*
Liver	Always enlarged	May be small
Spleen	Enlarged but not so marked	Enlarged
Ascites	Rare and late	Frequent symptom
Laboratory Findings	*Biliary Cirrhosis*	*Portal Cirrhosis*
Hyperbilirubinemia	Marked	Mild
Alkaline phosphatase	Marked elevation	Normal or slightly elevated
Serum cholesterol	Marked elevation	Normal or depressed
Cholesterol esters	Absolute values elevated or normal	Usually depressed
Serum phospholipid	Elevated	Normal or depressed
Total protein	Elevated or normal	Normal or de*pressed*
Gamma globulin	May be markedly elevated	Elevated but *not so high*
Beta globulin	Frequently elevated	Usually normal
Liver Biopsy	*Biliary Cirrhosis*	*Portal Cirrhosis*
Bile stasis	Present	Usually absent
Bile lakes	*Frequently* present	Absent
Pericholangiolitis	*Frequently* present	Usually absent
Fatty metamorphosis	Absent	*Frequently* present
Bile duct hyperplasia	May be marked	M*oderate*
Nodular regeneration	Scanty	Marked
Necrosis	*Usually not* marked	May *be marked*

jaundice (hepatocellular injury) It is important to evaluate and localize the level of biliary obstruction since the secondary type is amenable to surgery while the primary type can be treated only medically The salient differential features of these two have been outlined Cholangiography may have to be resorted to to rule out posthepatic obstruction this procedure can be done with the patient under local anesthesia and should be done in cases in which there is the slightest possibility of an extrahepatic obstruction

Hepatic enlargement if accompanied by minimal or mild jaundice requires differentiation from other hepatic diseases including hepatic syphilis and tuberculosis primary and secondary neoplasms and cysts of the liver These are discussed in the appropriate sections

In infants and children the disease may occasionally have to be differentiated from von Gierke's disease and erythroblastosis foetalis In von Gierke's disease jaundice is uncommon while the childhood form of biliary cirrhosis is always accompanied by deep icterus The peculiarities of carbohydrate metabolism in glycogen storage disease described in Chapter 75 should help clarify the issue In erythroblastosis foetalis the prehepatic nature of the jaundice is evident from the excessive amount of urobilinogen in the feces and urine the anemia and the blood group of the parents

In patients with xanthomatosis and hyperlipemia differentiation from other lipidoses must be made These other lipidoses include familial hypercholesterolemic xanthomatosis *hyperlipemia with secondary eruptive xanthomas* idiopathic and symptomatic type and normocholesterolemic xanthomatoses such as *the Schuller Christian syndrome* Gaucher s disease as well as Niemann Pick s disease must be differentiated because of their hepatosplenomegaly The diagnostic features of these are mentioned briefly here some are described in greater detail in Chapter 76 because they involve the liver per se

Patients with familial hypercholesterolemic xanthomatoses have various types of skin xanthomas moderately elevated cholesterol and lecithin levels and a definite familial history There is no jaundice no hepatosplenomegaly and no liver disease Only when liver disease develops in a patient with this syndrome in addition to the primary lipid metabolic disturbance should this condition be in any way confused with biliary cirrhosis

Idiopathic hyperlipemia with secondary xanthomas can be easily differentiated because the serum is milky as a result of the increase of the neutral fat rather than cholesterol or lecithin The liver becomes enlarged in this condition and may show dysfunction but liver biopsy reveals a grossly fatty liver resulting from accumulation of neutral fat The secondary type of hyperlipemia has features similar to the primary type but is usually seen in uncontrolled diabetics or patients with chronic pancreatic disease

In the Schuller Christian syndrome (eosinophilic granuloma *with xanthomatosis) the* liver is usually normal and the blood shows a normal cholesterol level Niemann Pick s disease and Gaucher s disease are usually but not exclusively seen in children they are not primary diseases of the liver but disturbances of lipid metabolism in which splenic rather than hepatic enlargement predominates and different fractions of the blood lipids are altered in *biliary cirrhosis* (see p 448)

1 Onset
   a With colicky pain chills and fever
   b After biliary surgery
   c Associated with signs of a malignant neoplasm
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B Laboratory findings
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Ascites	Rare and late	Frequent s mp tom
Lab y F nd g	*B C h*	*P C ho*
Hyperb l r b ne nemia	Marked	M d
Alkal ne ph phata e	Marked elevat on	Normal or sl ghtly ele vated
Serum choles terol	Marked elevat n	Normal or de pre ed
Cholesterol es ters	Ab olute values elevated or normal	U uall depressed
Ser m p ho pho l p d	Elevated	Normal o d pre ed
Total protein	Eleva ed or nor mal	Normal or d pressed
Gamma globul n	May be mark edl elevated	Elevated b t not so h gh
Beta glob l n	Freq ently ele vated	Usua norm l
L B p	*B l a y C ho*	*P l C hosis*
Bile stas s	Present	Usuall ab ent
B le lakes	Frequently present	Absent
Per cholang o- litis	Frequently present	Usual ab nt
Fatty meta morphos s	Ab ent	Freq ntl present
B le duct hyper plas a	Ma be marked	Mode a e
Nodular regener ation	Scanty	Marked
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which is neither due to the gross destruction of the pancreas by inflammation nor by pigment deposition will be the subject of this section This problem will be further subdivided into two components (1) the influence of diabetes on the liver and (2) the influence of the liver on diabetes

Involvement of the liver in poorly controlled diabetic patients has been repeatedly observed This is especially true in children Marble and coworkers (1938) reported 60 diabetic children with extreme hepatomegaly The hepatic enlargement was presumed to be due to fatty metamorphosis Fatty liver was found at autopsy in some of these patients and is frequently observed in patients dying in diabetic acidosis Fatty livers have been observed by others in juvenile diabetics (Grayzel and Radwin) as well as in adults (Connor) Liver function in diabetes was investigated by Gray and associates by means of the colloidal gold test They found this test positive in 91 of 247 patients The derangement was found in all age groups but was more marked in the poorly controlled diabetics Leevy and coworkers using a group of liver function tests found some abnormality in 38 9% of patients studied while those with complications had a much higher incidence of hepatic dysfunction Zimmerman and coworkers found a high percentage of functional and morphological abnormality in their group of patients Others have found a low incidence of hepatic dysfunction among diabetics and when it occurred it was transient in nature (Frankel et al) Brown in a small group of patients found no hepatic abnormality

In spite of the lack of complete unanimity of clinical studies the bulk of evidence points to significant morphological and functional abnormalities of the liver in some diabetic patients What is the pathogenesis of this particular type of liver injury? In most cases the initial change consists of a fatty metamorphosis All observers except Zimmerman s group agree that hepatic abnormalities are observed most commonly in poorly controlled diabetics The fatty liver of diabetes is therefore akin to the fatty liver of starvation In both uncontrolled diabetes and starvation the organism s metabolic processes are dependent chiefly on combustion of fat and this is therefore analogous to an organism maintained on high fat diet The administration of insulin and an adequate diet has a lipotropic effect and the lipids are removed from the liver The administration of lipotropic agents alone would probably not have the desired effect except in rare instances where there is accompanying destruction of the exocrine portion of the pancreas as well (Grayzel and Radwin)

Improved treatment of diabetes with diets more akin to normal and the judicious use of insulin should result in a decreased incidence of fatty livers in diabetes The development of cirrhosis in these fatty livers has been suggested by Connor Of fourteen diabetic patients with fatty metamorphosis reported by Zimmerman and his group three showed histologic evidence of cirrhosis So there is a possibility of cirrhosis developing in this type of liver injury But in view of the fact that fatty liver probably has to exist for a long time before cirrhosis develops and diabetes nowadays rarely goes uncontrolled or untreated for a long period of time it is more likely that the cirrhosis is a concomitant factor or precedes the diabetes

Role of the Liver in the Pathogenesis of Diabetes

This leads us into the next problem namely the effect of liver injury in the production of diabetes The role of the liver in the control of blood sugar has been ably delineated by Soskin and Levine in their book on carbohydrate metabolism The liver is the central controlling organ involved in maintaining a normal blood sugar It has been demonstrated that depancreatized dogs will respond to a large dose of sugar with a normal glucose tolerance curve when a constant supply of insulin is administered However the hepatectomized animal will give a diabetic glucose tolerance curve under the same experimental conditions A normally functioning liver therefore is essential for maintaining a normal blood sugar in the face of variations in carbohydrate intake Even in the presence of a normal source of insulin the liver is needed to remove

X The Role of the Endocrine Glands in Diseases of the Liver, Hepato-Renal Relationship

On teleologic grounds one would expect the liver the chemical power house of the body to have an intimate inter relationship with the chemical activators of the body the endocrine glands The liver with its enormous influence on the metabolism of food is merely one link in the chain controlling these processes the endocrine glands are the other links The islets of Langerhans of the pancreas the pituitary the thyroid the adrenals and gonads influence and in turn are influenced by the liver There is therefore a reciprocal relationship and normally it is in a state of finely adjusted equilibrium In a morbid state when there is either overactivity or underactivity of one or several of the endocrine glands or there is hepatic injury this equilibrium is destroyed the resultant biochemical abnormality contributes to further physiological and clinical disturbances

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The Role of the Liver in Diabetes and Hypoglycemia

The Liver in Diabetes Mellitus

The *relationship of the pancreas to the* liver is involved in these clinical states (1) in chronic pancreatitis and lithiasis (2) in hemochromatosis and (3) diabetes mellitus Like all other phases of medicine these three *are intertwined and* yet they present primarily different problems In chronic pancreatitis the exocrine apparatus of the pancreas is chiefly involved while the endocrine (insulin) secreting portion of the gland is only occasionally abnormal and the pathogenesis of the distinct type of liver injury is discussed on page 314 In hemochromatosis there is both *diabetes and hepatic cirrhosis* and in the fully developed disease the disturbed physiology of each influences the other however both organs are damaged by a common etiologic factor (p 535)

The *relationship of the liver* to diabetes

placed on high protein high carbohydrate diet and 50 units of insulin daily The insulin was progressively reduced and finally discontinued and he remained aglycosuric on a 3000 calory diet The fasting blood sugar as well as the glucose tolerance test returned to normal This happy state of affairs continued until he went on a furlough and a liquid diet composed chiefly of ethanol replaced the carbohydrates and proteins He again became jaundiced developed acidosis and was readmitted as a diabetic This individual diabetic was curable by treatment directed toward his damaged liver During one of these episodes he developed an acute pancreatitis suggesting the multiplicity of etiologic factors

It may be argued that liver disease may have a non specific effect like an infection in activating the diabetes in a potential diabetic and as soon as the liver disease is cleared up the diabetes again becomes subclinical however because of the intimate role of the liver in regulating carbohydrate metabolism I am inclined to hold the opinion that liver dysfunction plays a specific role The damaged liver may produce hypoglycemia because of lack of glycogen storage in the liver The damaged liver may likewise produce post prandial hyperglycemia because of sluggish removal of sugar from blood and impaired glycogen storage Why can t a damaged liver with adequate glycogen stores discharge glucose at an abnormally rapid rate (overproduction) and thereby produce fasting hyperglycemia?

The Influence of Liver Disease on Established Diabetes

In addition to certain types of liver damage in diabetes and the production of diabetes in certain types of liver damage the liver may play another role in this disease that of changing the course and severity of the disease It can be readily understood from an analysis of the role of the liver in maintaining the normal blood sugar that hepatic disturbance engrafted on pre existing diabetes may make the disease better or worse Since the breakdown of liver glycogen is largely responsible for the elevated blood sugar in the fasting state damage to the liver or displacement of the liver glycogen by fat may result in an apparent improvement in the diabetes This phenomenon was noted in depancreatized dogs When fatty liver developed in these animals their need for insulin decreased A similar situation may be observed in clinical diabetes Adults diabetic in whom hepatic damage is most likely to be present as a rule have milder diabetes than children

Usually when liver damage occurs in a diabetic the carbohydrate tolerance becomes worse I have frequently observed well controlled diabetics suddenly develop marked glycosuria and hyperglycemia without change in management On careful examination a slight icteric tinge hepatic tenderness and enlargement heralds the onset of hepatitis The reason for the deterioration in carbohydrate tolerance is due to defective glycogenesis in the damaged liver The liver cannot respond efficiently to the two stimuli to glycogenesis insulin and elevated blood sugar These are the hepatic insensitive patients of Sherlock They require more insulin for proper control of the diabetes but it must be remembered that they should receive an abundance of carbohydrates and proteins as well In other words the treatment of the diabetes should not be at the expense of the liver disease

The differential diagnosis between hepatic and pancreatic type of diabetes is not as important now as it has been in the past since high fat diets which can be deleterious to liver disease are no longer recommended for diabetes This differentiation is nevertheless of interest since intensive treatment with an abundance of carbohydrates and proteins may rapidly improve the hepatic diabetes A study of the liver with liver function tests and liver biopsy will aid immeasureably in detecting liver disease If both of these procedures are normal one can hardly attribute any significance to an undetectable liver disease unless some clinical sign points to it such as hepatomegaly and splenomegaly

Laboratory studies of the carbohydrate metabolism may shed some light on this problem The intravenous glucose tolerance test using one third gram of glucose per kilogram of body weight may be helpful in liver disease

excess glucose from the blood after a meal and supply glucose to the blood during fasting. So a hepatectomized animal rapidly goes into hypoglycemia during fasting and shows very high blood sugars immediately following carbohydrate ingestion. These marked swings in blood sugar are ordinarily not seen in clinical liver disease because of the tremendous reserve power of the liver, but abnormal carbohydrate tolerance tests are signs of liver dysfunction (p. 20).

Soskin and his coworkers have demonstrated that experimental diabetes in the dog may be changed from the insulin sensitive to the insulin resistant type of diabetes by damaging the liver. The depancreatized dog which shows a normal glucose tolerance curve while receiving constant injection of insulin will develop a diabetic curve when the liver is damaged by a toxin. The role of the liver in the maintenance of the normal glucose tolerance curve was dramatically demonstrated by producing progressive liver damage which in the early stages showed mild diabetic curve; with progression of the damage, the curve becomes more "normal" and finally markedly "diabetic" or "super normal" (Soskin and Mirsky, 1935). By damaging the liver with phosphorus, Althausen and Thoenes have shown that initially the dextrose tolerance curve becomes "diabetic," later it approaches normal and finally becomes "super normal," i.e., hypoglycemia develops.

These animal experiments have important clinical connotations. They suggest that in liver damage, carbohydrate tolerance may be normal, diabetic or super normal, and these differences do not necessarily depend on the degree or type of liver damage. Can diabetes mellitus then result from certain types of liver dysfunction? This depends on the definition of diabetes. Diabetes is a complex disease of multiple or unknown etiology. While it has been associated chiefly with dysfunction of the pancreas, dysfunction of other endocrine glands contribute to its genesis (Ricketts, Soskin). The liver, with its critical role in maintaining the blood sugar, can disturb carbohydrate metabolism sufficiently to produce hyperglycemia and occasionally glycosuria.

Lande and Pollock (1935) reported hyperglycemia and glycosuria requiring insulin in three patients with biliary tract obstruction. On the removal of obstruction, the carbohydrate abnormality disappeared. Leevy and coworkers (1950) found among a group of diabetics with hepatic dysfunction 15 who were primarily liver disease with secondary disturbance of carbohydrate metabolism. More recently (1952) these workers have reported ten alcoholic patients with hyperglycemia and glycosuria who responded to a hepatic type of regimen without insulin. Strouse and coworkers succeeded in improving the carbohydrate tolerance in a group of older patients (diabetics) with suspected hepatic disease by dextrose infusions and a minimal amount of insulin. I cannot agree with the sweeping statement of Taub and coworkers that all middle aged diabetics are primarily instances of hepatic dysfunction with secondary disturbance of carbohydrate metabolism. There is undoubtedly a difference between the juvenile labile diabetic and the adult stable diabetic and this difference may at least in part depend on liver dysfunction in the adult. Confirmation of this opinion comes from Sheila Sherlock's laboratory (Bearn et al., 1951). They studied the two types of diabetics by means of hepatic vein catheterization and liver biopsy and found that the young diabetics have histologically normal livers and respond to insulin administration with a marked fall in glucose output (hepatic sensitive), while the older diabetics showed morphological abnormality of the liver and did not respond to insulin administration with marked fall in glucose output (hepatic insensitive).

I have repeatedly seen patients with obvious liver disease show abnormal glucose tolerance tests, hyperglycemia and occasional glycosuria. Fasting hyperglycemia and glycosuria is rare. Although ketosis is very rare, I recollect a middle aged army sergeant who partook of alcoholic beverage beyond the specification of Army regulations. He entered the hospital with hyperglycemia, acidosis, ketonuria and jaundice. The liver was large and quite tender. The administration of insulin and glucose brought him out of acidosis. He was then

placed on high protein high carbohydrate diet and 50 units of insulin daily The insulin was progressively reduced and finally discontinued and he remained aglycosuric on a 3000 calory diet The fasting blood sugar as well as the glucose tolerance test returned to normal This happy state of affairs continued until he went on a furlough and a liquid diet composed chiefly of ethanol replaced the carbohydrates and proteins He again became jaundiced developed acidosis and was readmitted as a diabetic This individual diabetic was curable by treatment directed toward his damaged liver During one of these episodes he developed an acute pancreatitis suggesting the multiplicity of etiologic factors

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the hyperglycemia generally disappears two hours after administration of the glucose In pancreatic diabetes the hyperglycemia is prolonged If the results are not clear doubling the dose of glucose may separate the two conditions more definitely The greater hyperglycemia attained with the larger dose of glucose may improve the glucose tolerance curve in hepatic disease by its greater stimulation of glycogenesis but in the purely endocrine diabetes the curve should become more abnormal (more diabetic) In severe liver disease with severe carbohydrate abnormality this may not help but in those cases the presence of liver disease should be obvious

The glycogen storage test may be of help In this test a blood glucose rise is evoked by the administration of adrenalin (p 21) In normal individuals this rise averages 50 mg % in pancreatic diabetes 90 mg % while in hepatic diabetes and in liver disease in general the response is below normal 15–20 mg %

In addition to these tests the therapeutic test is simple and instructive A rapid improvement in the carbohydrate tolerance on high carbohydrate diet with a minimum of insulin is suggestive of hepatic disturbance as a background for the diabetes

The Role of the Liver in Hypoglycemia

The liver plays a role in producing hypoglycemia as well as hyperglycemia That liver failure is capable of producing hypoglycemia is dramatically demonstrated by the profound and rapidly fatal hypoglycemia after hepatectomy Hypoglycemia occurs in the massive hepatic necrosis of yellow fever (p 245) toxic hepatic necrosis and glycogen storage disease In any injury accompanied by massive necrosis of liver cells be it due to an infectious agent or toxin hypoglycemia may result from lack of viable parenchymal cells capable of storing glycogen and later converting it into glucose Hypoglycemia may occur in other diffuse liver diseases such as infectious hepatitis portal cirrhosis diffuse carcinomatosis and suppurative cholangiolitis with miliary abscesses While in these conditions the absence of glycogen in the liver is probably the chief factor in the genesis of the hypoglycemia a defect in the phosphatase reaction may impede the breakdown of the glycogen present In (Von Gierke s) glycogen storage disease the over abundant glycogen cannot be broken down *into glucose for the reasons explained* (p 558)

The characteristic feature of hepatic hypoglycemia is that it is accompanied by postprandial hyperglycemia Likewise the glucose tolerance test shows an initial hyperglycemia followed after four to six hours by hypoglycemia The reasons are obvious the damaged liver has difficulty with glycogenesis as *well as gluconeogenesis The initial* hypoglycemia in alloxan poisoning is due to liver damage

62—The Liver and Thyroid Activity

That thyroid overactivity is conducive to liver injury has been suspected for nearly a half century. David Marine in 1911 found *atrophic cirrhosis in four of six patients with* exophthalmic goitre of long standing. Indeed there were more reports and greater interest in this problem in the early literature than now. The greater difficulty in diagnosis and treatment during the earlier period resulted in a prolonged impact of the hyperthyroid state on the liver. In the more recent literature the interest is focused chiefly on the pathogenesis of the lesion.

The incidence of hepatic injury in hyperthyroidism varies in different series and this variation emphasizes that the hepatic lesion depends primarily on (1) the severity, (2) the duration and (3) the complications of thyrotoxicosis.

For this *reason the postmortem series represent* the highest incidence of the most advanced type of hepatic damage. Habán found cirrhosis in 38.8% of 36 cases of exophthalmic goitre. Cameron and Karuntaratne found changes varying from fatty metamorphosis to foci of necrosis and cirrhosis. These workers reported that ten of their 30 cases showed evidence of cirrhosis. Shaffer found only six cases of cirrhosis (25%), two of which were severe, among his 24 cases of hyperthyroidism. Beaver and Pemberton found 64 instances of cirrhosis among 107 patients with hyperthyroidism. The cirrhosis was severe in 16 and mild in 48. Moschcowitz, in his series of 31 patients who died at the Mt. *Sinai Hospital of New York* with a diagnosis of toxic or exophthalmic goitre, 11 (35.5%) were found to have cirrhosis. In addition to the lesions noted above, acute yellow atrophy (Kerr and Rusk), lymphocytic infiltration and bile duct proliferation suggestive of hepatitis (Warthin) have been described. In contradistinction to the above, liver biopsy, in the average case of hyperthyroidism fails to show significant morphological changes.

Evidence of hepatic dysfunction in clinical cases of hyperthyroidism is also abundant. The disturbed galactose tolerance test in hyperthyroidism may in part depend upon hepatic injury (Althausen, p. 22). Jaundice has been reported in patients with hyperthyroidism, but the possibility that this may have been due to concomitant hepatitis is, of course, a possibility (Eder 1906, Mahorner 1934). Maddock and coworkers in their study of patients with thyroid crisis found a hyperbilirubinemia of over 3 mg.% and bromsulfalein dye retention of over 10% in 61% of 13 patients. Bartels found decreased total serum protein in 63% of a group of patients with hyperthyroidism. The decrease was chiefly due to the depressed *serum albumin since the globulin remained* normal. These protein abnormalities were correlated better with the clinical picture than with the basal metabolic rate or duration of disease, and they returned to normal three months postoperatively. The hippuric acid synthesis test has also been found impaired in patients with hyperthyroidism (Bartels and Perkin, 1937) (Boyce and McFetridge, 1938).

Experimental Observations

There is an abundance of experimental evidence which points to the role of thyroxin in the production of liver damage. Central necrosis has been produced in animals by a combination of anoxia and excessive thyroid feeding and albino rats were found more susceptible to chloroform intoxication when rendered hyperthyroid by injections of crystalline thyroxin (McIver and Winter). The pathological changes in the liver of choline deficient rats can be retarded by thyroid deficiency. Thyroid feeding

hastens death *of these animals but the livers* showed little fat and no *necrosis (Handler* and Follis)

In general experimental evidence points to the deleterious effect of excessive amounts of thyroid on the liver However *there are some* observations that point to a salutory effect of the normal thyroid on the liver Thus Chaikoff and coworkers developed fatty and cirrhotic livers in hypophysectomized and thyroidectomized dogs, who were maintained on an adequate diet Cirrhosis was *not* observed after thyroidectomy alone Canzonelli and coworkers found that thyroxin *stimulates* liver regeneration by mobilizing nucleic and ribonucleic acid, which are thought *essential* for regeneration This *is not contradictory* since one would expect the normal *function* of the various glands of internal *secretion to provide the proper environment for various* essential processes but the over production of a hormone would produce damage somewhere These observations suggest that *in hypothyroidism the liver* may show *impaired regen*eration and a tendency to fatty metamorphosis It is not uncommon to see the hypo and hyper *function* of a gland to produce apparently similar disturbances

Pathogenesis of Liver Disease

How does hyperthyroidism produce its deleterious effect on the liver? The possibilities that we must consider are (1) direct toxic effect on the liver (2) circulatory changes in *the liver (3) anoxia* (4) *dietary* deficiency and (5) increased susceptibility to infection

When we speak of direct toxic effect of any agent we speak in general and in ill-defined terms *We mean that an injury is produced by* a certain agent but do not delineate the basic disturbance causing the injury We do not answer the following pertinent questions Does the substance *interfere with some vital enzy*matic process and if so in what way? Does the substance interfere with oxygen consumption by the cell or deprive the cell of some vital enzyme or vitamin? *In other words the* assumption of a toxic effect simply demands that we look for the mode of action of the toxin Thus, the increased susceptibility of hyperthyroid rats to chloroform poisoning could be construed as a synergistic effect between two poisons but actually leads us to look for another possibility

Circulatory Factor

The increased demand of the tissues for oxygen results in well known alterations in *circulation* There is an increase of cardiac output pulse pressure and circulatory rate *Moschcowitz in his excellent analysis of the problem* eloquently places the blame of the hepatic changes at the door of the altered circulatory dynamics His thesis favors disturbed *hepatic circulation* as the responsible factor for this lesion He likens the cirrhosis in hyperthyroidism to cardiac cirrhosis The difference consists in the precise location of the circulatory disturbance In cardiac failure the *increased* pressure makes the first imprint around the central vein which is a tributary of the hepatic vein while in hyperthyroidism the most vulnerable area is the periphery of the lobule where the sinusoids receive their blood from the hepatic artery In cardiac cirrhosis the lesion i most marked around the central vein while in hyperthyroidism the lesion is predominately at the periphery of the lobule (interlobular)

Moschcowitz found the progressive morphological changes in keeping with this hypothesis Marked dilatation of capillaries were found early and this was so marked as to result in *focal hemorrhage* eventual *compression* and dissociation of adjacent hepatic cords Eventually this leads to fibrosis round cell infiltration and the dilated capillaries give the area an angiomatous appearance The density of the fibrous tissue increases with the duration of the process In addition to the above changes fatty metamorphosis and focal necrosis and increased blood pigment are found in the parenchymatous cells

Anoxia

This beautiful theory seems reasonable enough But is there evidence of increased blood flow through the liver? Recent evidence

points to the contrary Myers and coworkers studied hepatic blood flow in patients with hyperthyroidism by means of the bromsulfalein extraction method and found that in spite of increased cardiac output the hepatic and splanchnic blood flow were not increased However the splanchnic oxygen extraction was even greater than would be expected from the increased metabolic rate of the body as a whole This greater demand for oxygen with the apparent increased need but the lack of increased supply could easily result in oxygen deficit especially in the centrolobular areas And indeed centrilobular necrosis has been seen in certain instances of hyperthyroidism The anoxic theory is more in keeping with this type of lesion and is supported in animal experiments in which anoxia augmented the hyperthyroid liver injury (McIver and Winter)

Dietary Deficiency

The increased metabolic rate results in increased utilization of foodstuffs including vitamins (Spellberg and Keeton) This increased utilization may create a relative deficiency unless an increased supply of essential nutrients is maintained Thus the liver may become depleted of glycogen a shortage of lipotropic agents and sulfur containing amino acids may be created and this in turn results in hepatic injury An abundance of carbohydrates has been advised in the treatment of hyperthyroidism and is thought to be a bulwark against the development of thyroid crisis Supplementary vitamins have been advocated for the same reason A high protein intake has been discouraged because of the specific dynamic action of proteins tending to raise the basal metabolic rate however in view of the increased protein catabolism and the need of proteins for the protection of the liver this food substance should also be maintained at a high level

Infection

In view of the fact that some patients with hyperthyroidism and liver damage are complicated by infection the role of this factor in producing the liver injury has to be considered Infection by itself is productive of hepatic damage (Section VI) moreover hyperpyrexia increases anoxia as well as dietary insufficiency by increasing the demand

Pathogenesis of Liver Disease in Hyperthyroidism—Summary

1 Circulatory Factor
- **a Increased cardiac output**
- **b Increased pulse pressure**
- **c Increased circulation rate lead to peripheral lobular (perilobular and periportal) sinusoidal congestion and dilatation followed by**
  - **hemorrhage**
  - **pressure atrophy**
  - **round cell infiltration and fibrosis**

2 Anoxia resulting from
- **a increased demand for O**
- **b hepatic and splanchnic blood flow not increased leads to centrolobular necrosis**

3 Dietary deficiency
- **a increased metabolic rate results in**
- **b increased demand for nutrients creating**
- **c deficiency of essential factors**
  - **1) lipotropic agents**
  - **2) S amino acids**
  - **3) vitamins**

4 Infection

May act directly on the liver or by increasing the other factors
- **a anoxia**
- **b demand for foodstuff and**
- **c circulatory disturbances**

Summary

We may therefore say without hesitation that hyperthyroidism tends to produce liver damage In terms of the thyrotoxicosis it is more likely to occur in the more toxic complicated and prolonged disease Circulatory changes and anoxia are probably the chief avenues through which the damage is produced but as in so many instances of hepatic injury multiple pathways lead to liver damage and dietary insufficiency as well as infection may be involved

The prevention and treatment of liver damage in hyperthyroidism should aim toward (1) early diagnosis of primary disease and

appropriate treatment (2) attention to circulatory adjustment (3) prevention of anoxia by decreasing muscular activity and the use of oxygen during and after anesthesia, (4) strict attention to diet, (5) increased intake of essential nutrients (6) prevention and prompt treatment of infection and (7) avoidance of hepatotoxic agents

63 — *The Role of Estrogens and Androgens in Liver Disease*

THE female and male sex hormones will be considered together since the final effect on the organism depends upon their relative concentration This question of gonadal disturbance in liver disease is an important one in view of the frequency of clinical alterations directly attributable to sex hormone imbalance *The other phase of the problem that is of* interest is whether the hormonal disturbance is secondary to the liver disease or primary And if secondary what effects if any do the gonadotropic hormones have on liver physiology and pathology?

Clinical Changes Attributable to Gonadotropic Imbalance

In clinical liver disease especially in cirrhosis feminizing features have been noted in the male and *menstrual disturbances in the* female which can be attributed to disturbed sex hormone level The changes are especially conspicuous in the male and consist of (1) pectoral alopecia (2) loss of axillary [illegible] (3) loss of libido (4) impotence (5) [illegible] testicular atr[illegible] (7) [illegible]gy

Spider ne[illegible] mark[illegible] have also [illegible] to [illegible] balance (p 405

Since [illegible] is an secondary sexua[illegible] stic [illegible]ecia can be [illegible] a [illegible]

feature Pectoral alopecia is so frequently seen in portal cirrhosis that I consider it one of the commonest findings and one helpful in establishing a diagnosis However unlike the other feminizing features it antedates the onset of cirrhosis It seems to be a sign of a constitutional disturbance which is indicative of a pre*disposition to cirrhosis Since it precedes the* development of cirrhosis and all patients I have questioned about this point insisted that *the pectoral alopecia was always present* it cannot be due to the liver dysfunction If the pectoral alopecia is due to increased estrogen/androgen ratio this endocrine imbalance must then precede the development of liver disease a hypothesis for which there is no evidence

Loss of axillary hair may develop secondarily *to the development of cirrhosis but it* on *occasion precedes the cirrhosis along* with the pectoral alopecia Impotence loss of libido sterility and testicular atrophy develop as the cirrhosis progresses Loss of libido and impotence have been considered a feature of chronic alcoholism but are probably secondary to the concomitant cirrhosis Impotence and loss [illegible] by themselves may be psychic in [illegible] accompanied by testicular [illegible] and aspermia are conclu[illegible] organic changes Lloyd and [illegible]s of libido and potency loss

of axillary hair and testicular atrophy in increasing frequency in the more severe cirrhotics 75% of patients in whom testicular size could be determined showed testicular atrophy This finding is more common in the older age group Morrione found testicular atrophy in 16 of 8 patients with Laennec s cirrhosis He did not feel that alcohol per se is a contributory factor Other cases of hepatic failure likewise show testicular atrophy In this group as well the testicular atrophy was more common after the age of 50 and was related to the severity of liver damage

Gynecomastia is another important finding in chronic liver disease The description of gynecomastia by Silvestrini in 19 6 and testicular atrophy by Corda in 1925 in patients with portal cirrhosis has given rise to the term the Silvestrini Corda syndrome to which Eppinger added loss of axillary hair Gynecomastia was found by Lloyd and Williams in 4 % of 55 patients The incidence of gynecomastia is related to the severity of cirrhosis and varied from none in two mild cases of cirrhosis to o of 26 patients with severe cirrhosis There is little doubt that this finding is related to the severity of cirrhosis

A gynecomastia of another type so called refeeding or nutritional gynecomastia has been reported by Kark and coworkers Klatskin and coworkers and Musselman This type of gynecomastia may occur in the absence of liver disease is apparently not a feminizing feature and occurs during the period of improved nutrition after a period of prolonged starvation Its pathogenesis is entirely different from the gynecomastia of cirrhosis

Cutaneous arterial spiders have been noted to occur during pregnancy and to disappear after delivery Bean succeeded in developing the e spider nevi in two of three chronic alcoholics and palmar erythema in one by means of estrogen administration The e observations suggest that spider telangiectasis as well as palmar erythema of liver disease may be due to hormonal imbalance

Clinical Significance of Gonadal Disturbance in the Female

The feminizing features of the gonadal disturbance in the male are o dramatic and impressive that much of the clinical literature neglects the changes in the female One would expect hyperestrogenism in the female as well as in the male and this assumption is confirmed by the experimental observations of Furlong and coworkers that female guinea pigs exposed to carbon tetrachloride increase their urinary estrogen excretion to 350 times the normal value This enormous increase of estrogen excretion levels off to 3 7 times the normal amount This subsequent decrease of estrogen excretion may be due to an inhibition of endogenous estrogen formation

The more subtle clinical features of hyperestrogenism in the female consist of ovarian dysfunction expressing themselves in (1) menstrual disturbances (a) amenorrhea (b) dysmenorrhea (c) functional bleeding (2) sterility (3) breast changes (a) cystic mastitis (b) benign metaplasia and (4) acne

Amenorrhea and loss of fertility may occur in any serious infection or profound malnutrition and avitaminosis The decision as to which is the responsible or initiating mechanism in the endocrine disturbances—the malnutrition or the liver disease—is a difficult one Indeed the inter relationship between diet hormones enzymes and hepatic function is as intimate as the link of a circular chain o that one cannot tell which one precedes the other There is no doubt that malnutrition can directly effect the function of the endocrines as well as produce liver injury the latter in turn may produce further endocrine changes In most instances in the male with cirrhosis the liver disease initiates the gonadal imbalance Malnutrition may play a secondary role especially by its effects on the pituitary gland There is no reason why the same sequence of events may not occur in the female

Long and Simmons reported on two female patients with menstrual disturbances associated with chronic liver disease One of these was an alcoholic with associated malnutrition Both patients showed improvement in their menstrual cycle as the liver disease improved One patient howed masculinizing features male hair distribution enlargement of clitoris and small atrophic breasts No hormonal studies were done to explain this apparent masculinization

Masculinizing changes in the female cannot be explained on basis of increased estrogen and there is no reason to suspect increased androgen in the female. Lloyd and Williams had a varied experience with their female patients in regard to clinical endocrine disturbances. Some were post menopausal, others had oopherectomy prior to onset of cirrhosis which obscured the possible effect of the liver on gonadal physiology. They also noticed masculinizing features such as atrophic breasts and masculine hair distribution. However several patients had excessive menstrual bleeding, two of these had hyperplastic endometrium on biopsy and one had nodular breasts.

Other clinical observations had been interpreted as indicative of a disturbed gonad liver relationship in the female. The high incidence of and mortality from acute hepatitis in menopausal females reported from Scandinavia (Alsted) raises the possibility of a protective action of estrogens on the liver. This theory is highly conjectural. It was suggested by Alsted that the hepatitis differs from the usual infectious hepatitis and the high mortality and age and sex distribution was attributed to the peculiarities of the virus (Chapter 38).

Some toxemias of pregnancy are accompanied by and attributed to hepatic necrosis. Acute yellow atrophy has in the past been more frequent in the female. Some forms of eclampsia resemble the hepato renal syndrome. What role if any the endocrine changes of pregnancy play in hepatic injury is not known but a cause and effect correlation is very doubtful. It is more likely that nutritional factors are responsible. The metabolic stress of pregnancy makes an increased demand on proteins, lipotropic substances, etc. A mild deficiency which results in no apparent clinical disease may bloom forth into serious hepatic damage because of this increased demand and relative augmentation of the deficiency. This hypothesis is supported by the greater ease with which nutritional hepatic necrosis is produced in the pregnant rat. This was demonstrated by Lindan when he noted that pregnant rats developed massive hepatic necrosis on a diet deficient in sulfur amino acids and tocopherol within 25-30 days while the non pregnant controls did not develop necrosis in 30 to 40 days. Sims found no evidence of increased demand for choline and methionine but changes in the liver and mammary gland developed rapidly in the deficient pregnant animals. Fink noted that the morphological changes in the liver and kidney of rats on a cystine deficient diet are similar to those seen in human eclampsia. Indirectly the endocrine equilibrium in the female may have an augmenting effect on nutritional liver damage because of the protein sparing effect of testosterone. Circulatory changes in the liver during pregnancy are apparently not implicated. Munnell and Taylor found the hepatic blood flow the same in pregnant and non pregnant woman.

The Role of the Liver in Regulating Sex Hormone Activity

The liver has the all important role of regulating the gonadal hormones and maintaining the proper balance between estrogens and androgens. The homeostatic role of the liver pervades the field of endocrine metabolism as well as that of the foodstuffs. The disturbance in the regulating efforts of the liver became particularly conspicuous in male patients. The estrogenic as well as the androgenic hormones are inactivated chiefly by the liver. The spleen and kidneys inactivate them to a small degree. From in vitro studies of rat liver slices this organ can metabolize enormous amounts of estradiol and other estrogens (Tagnon et al., Lieberman et al.). Normally the hormonal inactivation is so finely adjusted to their production that active circulating hormones are maintained at the proper level for normal stimulation of the end organs.

In liver failure if inactivation of the male and female sex hormones were equally impaired the ratio between them would remain the same and no clinical abnormality would result. It appears that estrogen inactivation is more readily impaired with resultant accumulation of excessive amounts of estrogens. The Biskinds pointed out that vitamin B complex deficiency does not impair the inactivation of testosterone but seriously impairs the inactivation of estrogens. Inactivation of estrone by rats is markedly impaired on a low protein diet

(Vanderline and Westerfeld 1950) The established sensitivity of the liver to protein deprivation suggests that the impaired inactivation of estrone is due to liver damage

Estrogens are not only inactivated by the liver but also excreted by the liver in the bile Cantarow and coworkers claim that inactivation of estrogen by the liver is inefficient and that most of this hormone is excreted in the bile However their data are based on intravenous injection of large doses (-50 000 i u) Others have found no estrogen in the bile of normal animals or small amounts after subcutaneous injections of hormone (Longwell and McKee) It is possible therefore that biliary excretion of the hormone is a reserve mechanism which comes into play when other methods of disposal are overburdened The method of inactivation of estrogenic hormone is probably via one or more of the following routes (1) dehydrogenation ( ) conjugation and (3) esterification (Glass)

The omnipotence of the liver is demonstrated by the observation that it is responsible for the synthesis of a lipo-protein bound estrogen—'estrolipoprotein —which is the circulating active form of the hormone This complex acts as a reservoir of the free estrogen (Roberts and Szego 1946)

Progesterone is likewise inactivated slowly by the liver Administration of progesterone by stomach tube to the rabbit results in a lower progestational response than when administered subcutaneously This is thought to be due in part to its inactivation by the liver (Masson and Hoffman) Moreover the injection of progesterone into the portal vein is less effective than subcutaneous injection further proof that the liver inactivates this hormone (Engel) Pregnandiol a metabolic product of progesterone is inactivated by the liver but neither stored nor excreted by it Pregnandiol accumulates in the a pro- hepa

urinary estrogen excretion or an elevation of estrogen blood values in patients with liver disease Glass (1950) presented a concise review of this subject but it may be of interest to the reader to hear of some detailed observations dealing with this problem Glass and coworkers (1940) found high free urinary estrogens in all but two of eight male patients with cirrhosis The two patient who had no free urinary estrogens showed no gynecomastia while all but one with free estrogen had gynecomastia These data suggest a cause and effect relationship between gynecomastia in liver disease and free urinary estrogens The urinary androgens were decreased These workers (Glass et al 1944) also found increased excretion of free estrogen in the urine after injection of estrone or estradiol into patients with cirrhosis The severity of the liver disease paralleled the amount of free estrogen excreted Bennett et al 1950 found abnormally high urinary estrogens in four of six patients dying from cirrhosis of the liver A high incidence of breast enlargement was noted in their group of patients In acute hepatitis estrogen excretion has been found increased during the acute phase of the disease with a return to normal during convalescence (Gilder and Hoagland)

The correlation of free estrogen excretion with gynecomastia has not been noted by all observers Thus while Rupp et al (1951) found high total estrogen excretion in 16 and high free estrogen excretion in 12 of 25 patients with liver disease this was not well correlated with gynecomastia Gynecomastia was present in some with low urinary estrogens and absent in others with high estrogens Pincus and coworkers (1951) noted high urinary estrogens excretion and delayed clearance of injected estrogen in about one third of the tests do on patient with liver disease There wa ever no correlation between these studies and other liver function tests, tween estrogen abnormalities and mastia Palmar erythema and ectasis were likewise poorly the abnormal estrogen metabo of correlation between e gynecomastia in a given validate the theory that th

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Testosterone

Not only is there increased estrogen but also decreased androgens in severe liver disease The decrease in androgens may be due to atrophy of the testis which in turn may be the result of hyperestrogenism or the androgen decrease may be due to disturbance of adrenal function The testis in liver disease is very susceptible to the action of estrogens (Morrione) The decrease in urinary androgen excretion has been mentioned The decreased 17 ketosteroid excretion repeatedly observed in chronic liver disease (Rupp et al 1951 Pincus et al 1951 and others) may be due to disturbed testosterone metabolism

West and coworkers (1951) studied the fate of intravenously injected testosterone in human beings They were impressed by the rapid disappearance from the blood of the hormone within five minutes less than 10% of the theoretical amount remained in circulation Enzyme systems in the liver are apparently responsible for changing the testosterone molecule into other compounds which are finally excreted in the urine In the normal individual 74% of the injected testosterone was accounted for by the increase in conjugated 17 ketosteroids in the urine (West et al) In liver disease the preferred route of disappearance of testosterone is not by way of 17 ketosteroids which does not increase markedly in the urine after testosterone injection This alternate route of metabolizing testosterone may in part account for the low 17 ketosteroid excretion in liver disease and this in turn is indicative of disturbed testosterone metabolism in liver disease

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ation alone These workers made careful histologic examinations of the hypothalamus and found significant changes in this area They therefore concluded that the hypothalamic injury with the consequent change in appetite and food intake was responsible for the hepatic changes

Influence of Liver Disease on Anterior Pituitary

The effect of liver disease on the function of the anterior pituitary is one of inhibition or depression This effect is undoubtedly dual in causation Inanition and malnutrition which is so commonly present in chronic liver disease may by itself damage and inhibit the activity of the pituitary gland The hyperestrogenism of hepatic disease inhibits the gonadotropic secretions of the pituitary gland

Nutritional injury or depression of the pituitary gland would produce its effect on the entire gland pan hypopituitarism with a decrease of all of its hormonal activities while the depression resulting from liver disease is more selective The increased active circulating estrogens depress the elaboration of the gonadotropic hormone In the male this removal of gonadotropic stimulus to spermatogenesis and

THE MECHANISM OF ENDOCRINE IMBALANCE IN LIVER DISEASE

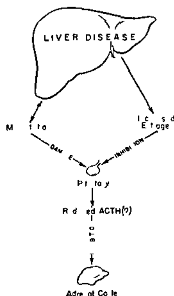


Fig 8

androgen elaboration would further augment the feminizing features described before Actually the suppression of pituitary activity may be due to both factors and therefore one may expect hyposecretion of other pituitary hormones in addition to the gonadotropic hormones (Fig 8)

Gonadotropic Hormones in Patients with Liver Disease

The observed excretion of gonadotropic hormones in the urine in patients with liver disease is somewhat conflicting but not incompatible with the theoretical considerations described Rupp and coworkers found increased *follicle stimulating hormone* excretion in five of 25 patients with liver disease They felt that from their data there was no evidence that FSH excretion was influenced by liver disease Most of their patients had an excretion of less than six mouse units per 24 hours Lloyd and Williams noted urinary gonadotropin excretion of less than five rat units in three of their patients Pincus and coworkers found no gonadotropic activity in 35 of 44 specimens obtained from 28 patients This is evidence of depressed pituitary gonadotropic activity but many of these had low estrogen excretion as well and therefore in only a few could the depressed gonadotropic activity be correlated with hyperestrogenism

While the observations related above provide meager confirmation of the theory of gonadotropic inhibition by the hyperestrogenism of liver disease they do not refute it It is possible that urinary gonadotropic studies are not adequate evidence of suppression of this hormone since even normally small amounts are excreted in the urine Moreover age variations must be considered since after menopause the normal gonadotropic secretion rises markedly and a so called normal excretion during that period of life is really low

The Relationship of the Adrenal Cortex to Liver Disease

The role that the adrenal cortex plays in liver disease is of timely interest to the physician in view of the increased use of cortisone and adrenocorticotropic hormones in the treat

ment of many diversified conditions including derangements of the liver However the importance of the adrenal cortex in intermediary metabolism makes mandatory its consideration in liver disease

Adrenal cortical hormones effect carbohydrate protein and fat metabolism and many of these effects are produced through the liver as the end organ Engel s recent comprehensive review is recommended to the reader who is interested in a complete analysis of this problem The effect of the adrenal gland on glycogen storage in the liver is evident from the rapid fall of liver glycogen in adrenolectomized animals (Long et al) Some evidence points to the inability of the liver to deaminize endogenous amino acids and convert them into glucose (Lewis et al) The reduction in protein catabolism is further evidenced by the decrease in urea nitrogen formation and excretion in fasting adrenolectomized animals although the defect in protein metabolism is largely extrahepatic the increased rate of protein synthesis and decreased rate of protein breakdown in these animals is of importance in relation to liver disease

There are interesting observations on fat metabolism that have a bearing on the subject at hand The effect of adrenocorticotropic hormone on the production of fatty livers has been mentioned It has been also demonstrated that cortisone can produce fatty livers in animal and that neither ketosis nor fatty infiltration can be produced in adrenalectomized animals (Levin and Farber) This type of fatty liver is not accompanied by protein sparing effects Wool and his associates demonstrated that both adrenalin and cortisone are needed for the production of an ethionine fatty liver

Sinaiko and Necheles produced focal necrosis and fatty degeneration in the liver of dogs by injection of desoxycorticosterone

Effect on Hepatic Regeneration

Berman and coworkers found that adrenalectomy inhibited the increase in size and multiplication of cell after partial hepatectomy along with reduction in fat and proteins However adrenocortical extract reversed this process and desoxycorticosterone acetate also hastened regeneration in these animals This speaks for a favorable effect of the adrenal cortex on hepatic regeneration However Drabkin observed that adrenolectomized animals on high protein diet showed greater capacity for regeneration after partial hepatectomy than normal animals Fasting animals or those on inadequate protein intake have difficulty with regeneration because of the disturbed endogenous protein metabolism

Effect of Hormones on Enzyme Content of the Liver

The relationship between enzymes and hormones in general and the liver in particular is one of the most fascinating phases of biochemistry The hepatic alkaline phosphatase increases after hypophysectomy and returns to normal level with growth hormone administration (Mathies et al) The effect *of hypophysectomy on the alkaline phosphotase of the liver* has been attributed to changes in carbohydrate activity in the liver but the possibility exists that it is a response to a particular type of damage to the liver The alkaline phosphatase of this organ is three time as high in the male as in the female rat (Lowe and Salmon) and this difference was thought to depend on the gonadal hormones This difference disappeared in the regenerating liver after partial hepatectomy A decrease of liver alkaline phosphatase has also been noted in induced hypothyroidism and in treatment with adrenal cortical extract (Vail and Kochakian)

Cholinesterase in plasma and liver of female rats increases at maturity probably due to the action of estrogens Cortisone decreases this increased cholinesterase concentration both in the liver and plasma This effect on cholinesterase may be an expression of the protein catabolic effect of cortisone Schweppe and associates studied the effect of cortisone on liver monamine oxidase an enzyme which shows trends opposite to those of cholinesterase Monamine oxidase unlike cholinesterase shows greater activity in the liver of adult male than female rats Cortisone injection into male rats reduced the monamine oxidase to the level of the females

Adrenocortical Function in Liver Disease

A suppression of adrenocortical function has been postulated as an end result of the other endocrine disturbances in hepatic disease The sequence of events are illustrated in Fig 82

The reduction of urinary 17 ketosteroids to very low levels in patients with liver disease both acute and chronic has been noted by many observers This has already been alluded to (p 472) It has been pointed out that this reduction can be partially explained by reduction in and changes in testosterone metabolism however this reduction in 17 ketosteroids may also be an indication of deficient adrenocortical activity Kark and associates have assumed the reduction of this steroid in the urine of male patients to eunachoid levels, as due to adrenocortical deficiency in nitrogen fixing hormone The marked reduction of 17 ketosteroids in female patients (Eisenberg et al) suffering from liver disease can be even more plausibly attributed to adrenal failure Finestone and Shuman concluded on the basis of eosinophile response to epinephrin the hyaluronidase fluorescein skin test and 17 ketosteroid excretion that eight of ten patients with cirrhosis showed adrenocortical hypofunction The two that showed normal responses were markedly improved and had normal liver function tests

While dysfunction of the adrenal cortex in advanced liver disease may be accepted as proven hyposecretion of all the adrenal steroids certainly does not occur The decrease of sodium excretion in the urine (p 418) sweat and saliva is suggestive of an increase of elaboration of salt retaining steroids (desoxycorticosterone) Elevated corticoid excretion has been noted in patients with liver disease (Bongiovanni and Eisenmenger 1951 Kark et al 1951) Since as was pointed out by Kark and associates it is not possible at present to separate the mineral corticoids from glucocorticoids, one can only postulate that the former are increased in amount These workers noted an increase in water and sodium retention after ACTH administration in their cirrhotics and concluded that these effects were due to augmentation of mineral corticoid influence on water and salt metabolism These points must be clearly kept in mind when we discuss the use of these hormones in therapy

The reader should be reminded for the purpose of clear perspective that testosterone (p 576) as well as estrogen and progesterone have water and salt retaining effects (Thorn et al 1938 Taylor et al 1939) The known increase of the last two of these hormones in cirrhosis exert an influence on the water electrolyte disturbance Other factors entering into this problem will be discussed subsequently

Rationale of the Use of Cortisone and ACTH in the Treatment of Liver Disease

With the advent of any new potent therapeutic agent attempts are made to use it in many diversified diseases for which no specific therapy is known It is to be expected that many early enthusiastic observations should lead to later disappointments

Webster in 1950 reported the use of an extract of adrenal cortex in the treatment of nine patients with liver disease Since the potency and exact nature of his preparation were not stated the favorable impression expressed by him cannot be given its proper perspective Flink and Williams treated eight patients with cirrhosis with ACTH Three of these patients had cholangiolitic cirrhosis with elevated bile acids and pruritus The only notable effect was a depression of bile acid and improvement of pruritus No improvement either clinical or laboratory was noted in any of these patients The only chemical change of interest was a decrease in the elevated gamma globulin This seems to be a direct effect of the hormone on protein metabolism since I have noticed the same result in the treatment of patients with ulcerative colitis with cortisone

Holmes and Perceful noticed no improvement in two cases of chronic hepatitis while on cortisone therapy 23 other patients mostly rheumatoid arthritis were studied with liver function tests while on cortisone therapy They claimed no deleterious effects on liver function although considerable increase in thymol turbidity was noted This cannot be explained on the basis of non specific protein alteration since the globulin decrease mentioned abov

should decrease the thymol turbidity. Rifkin and coworkers reported favorable results from the use of corticotropin and cortisone in four patients with acute hepatitis. Since this disease is usually self limiting with conservative therapy, there is no proof that any important contribution was made by cortisone. The euphoria, improvement in appetite and defervescence are expected results from this therapy. Buff and coworkers found no significant effect from this therapy in one patient with serum hepatitis and one with biliary cirrhosis. They refer to the untoward effects of sodium retention and potassium loss.

Blahd and associates noticed a favorable effect on appetite and the sense of well being from cortisone and ACTH in patients with cirrhosis of the liver and in some cases a diuresis upon withdrawal of these substances. Patients with mild cirrhosis responded to these hormones in a similar fashion to normal individual, but those with advanced cirrhosis showed an increase of edema and ascites. Chapman and associates (195) noted no untoward effect from the use of these hormones in patients with cirrhosis providing sodium restriction was observed.

Some have referred to the glycogenetic effect of cortisone but actually this hormone as well as ACTH cause fatty infiltration of the liver in experimental animals (p. 304). Fatty changes in a patient treated with cortisone has been reported. This process was reversed after discontinuance of cortisone (Steinberg et al.). Water and salt retention in patients with liver disease can become very serious with the development of ascites and massive edema.

In general it seems to me the evidence from theoretical as well as clinical considerations points against cortisone and corticotropin as rational agents in the treatment of liver disease. One favorable report worthy of note is the one by Schwartz who observed that cortisone inhibits dietary hepatic necrosis in the rat. The inhibitory effect of these hormones on fibrous tissue proliferation is not an acceptable indication in liver disease since fibrosis occurs secondary to parenchymal destruction and is not the process to combat.

Cortisone and ACTH is dangerous in patients with liver disease because these hormones cause (1) fatty infiltration of the liver, (2) increased protein catabolism and (3) water and salt retention, situations which one struggles to counteract. These deleterious changes are more likely to occur with ACTH than with cortisone.

The most favorable effect to be attained from these hormones is their appetite stimulation; however it has been suggested that this effect is merely compensatory for their protein catabolic effects. For further discussion of the clinical use of these hormones see page 576.

The Role of the Posterior Pituitary in Liver Disease

The apparent imbalance of adrenocortical and other hormones adequately explain sodium retention in liver disease but edema and ascites is actually a problem in water retention. Sodium and water retention frequently but not always parallel each other. Defective water excretion in clinical and experimental liver disease is discussed elsewhere (p. 40). There is no doubt that at least in advanced liver disease there is an antidiuretic process at work. This consequently turns our attention to the antidiuretic hormone of the posterior pituitary, pitressin.

It may be well to clear up one point first, namely that the action of the mineral corticoids and pitressin in regard to electrolyte and water metabolism do not parallel each other but are actually antagonistic in some respects (Silvette and Britton 1938). The adrenal cortical hormone has a diuretic and pitressin has an anti-diuretic action. The antidiuretic effect of the cortical hormone is secondary to its salt retaining properties. On the other hand pitressin increases sodium excretion. It has been shown recently that one of the cortical hormones, desoxycorticosterone, is antagonistic to the posterior pituitary antidiuretic hormone with respect to sodium excretion, synergistic with respect to potassium excretion and has no influence on water excretion. Therefore an increase of antidiuretic hormone as well as mineral corticoids would satisfactorily explain both the water and salt retention.

While there is no absolute proof that there is an increase of effective pituitary antidiuretic *hormone* in liver disease there is evidence that an antidiuretic *factor* is present in excessive amounts and the possibility exists that it may be derived from the posterior pituitary The evidence pointing to the pituitary antidiuretic hormone has been admirably summarized by Ralli and Leslie An antidiuretic substance has been found in the urine and livers of patients with cirrhosis and animals with dietary hepatic injury (Hall et al) This substance when injected into a rat produced a similar antidiuretic effect to pitressin In most instances in which marked water retention occurs increased secretion of antidiuretic hormone is probably an important factor (Verney 1946) Increased amounts of antidiuretic factor has been found in the urine of patients with cirrhosis and edema by a number of observers no increase in antidiuretic activity of the serum has been found by Perry and Lyles (1953) The antidiuretic factor of the posterior hypophysis is destroyed by the liver (Eversole et al) this would suggest that the hepatic damage may allow an excessive accumulation of this hormone however the report of White and coworkers that pitressin seems to be inactivated at a normal rate by the damaged liver forces the conclusion that increased production must be involved

If there is an excessive secretion of the antidiuretic hormone *how is this excessive secretion brought about?* The neurohypophysis responds by *increased hormone secretion to* elevation of sodium concentration through the so called osmoreceptors Sodium chloride ingested by a normal individual is quickly excreted but a patient with liver disease does not excrete the salt so readily probably because of the excessive amounts of corticosteroids This increased sodium retention stimulates the *osmoreceptors more antidiuretic hormone* is elaborated and water as well as salt is retained Thus, the water and electrolyte disturbances seen in liver disease are best explained by combined adrenocortical and posterior pituitary dysfunction The diuresis of restricted salt intake can be much more readily explained by its effect on the elaboration of the antidiuretic hormone rather than the adrenocortical hormones for salt restriction causes increased secretion of corticoid but inhibits pitressin secretion

The increase of antidiuretic hormone secretion by stimulation of osmoreceptors with sodium elevation can be explained only when the serum sodium is elevated However many patients with cirrhosis and ascites have *hyponatremia It is of course* possible that under those abnormal circumstances the osmoreceptors become responsive to lower levels of sodium concentration It has been postulated from the work of Lewis and coworkers Leaf and Mamby and Strauss and associates that the secretory activity of the posterior hypophysis also responds to a volume receptor mechanism That is a decreased volume of cerebral blood flow results in continued stimulation of antidiuretic hormone secretion Eisenmenger (1952) postulates that in cirrhosis a reduced effective circulatory blood volume may be present in spite of an increased blood volume and this stimulates the volume receptor when the osmoreceptors are not stimulated by the low blood sodium Thus even in hyponatremia increased antidiuretic hormone is elaborated through this alternate stimulus

65 — *The Relationship of the Kidney to Hepatic Disease**

There are several facets of contact in derangements of the kidney and liver. This relationship will be discussed under three headings: (1) renal function in hepatic disease, (2) coexistence of renal and hepatic disease, and (3) hepatorenal syndrome.

Renal Function in Liver Disease

The first of these, renal function in hepatic disease, is intimately associated with the preceding discussion of water and salt metabolism in hepatic disease. For regardless of the mechanism that puts this process in motion, be they hormones of the adrenal cortex or posterior pituitary or a combination of the two, the kidney is the end organ concerned with excretion of sodium and water. What then is the basic disturbance in renal function that brings this about? Renal function dealing with excretion of electrolytes and water is complex and the various subtle details are by no means clear or settled; however, several basic principles are generally accepted and will be presented as such.

Renal excretion of sodium, as of many other electrolytes, is a balance between glomerular filtration rate and tubular absorption of sodium. Some reduction of glomerular filtration rate in patients with cirrhosis was found by several investigators (Farnsworth and Krakusin, Sims) in patients with cirrhosis and ascites. These reductions were not of the magnitude seen in renal failure. The observations of Leslie and Ralli are particularly important since they noted low filtration rates in their patients during the period of accumulation of ascites, but normal filtration rates after the disappearance of ascites. Some patients tested repeatedly showed this progressive change of glomerular filtration rate depending on the degree of ascites. This disturbed glomerular filtration may be accounted for on the basis of disturbed renal blood flow. The blood volume in patients with cirrhosis is not always elevated and may be normal or subnormal, but even if elevated the effective peripheral blood flow may be decreased. The low blood pressure in cirrhotics along with apparent dehydration and the action of the vasodilating mechanism (VDM) of Shorr may all conspire to produce low glomerular filtration. The similarity between the salt retention of cirrhosis and congestive heart failure even in respect to diurnal variation (Goldman) superficially suggests a circulatory factor.

Tubular Absorption of Sodium

As so frequently happens in medicine, the problem cannot be dismissed simply, for contradictory data are presented by other observers. Epstein and coworkers studied patients with cirrhosis and ascites and found normal filtration rates in many of these. In such instances increased tubular absorption must be accountable for sodium retention. Farnsworth likewise suggested that the almost complete lack of sodium excretion by some cirrhotics is best explained on the basis of tubular resorption of sodium. This selective sodium absorption by the renal tubules again suggests hormonal control. The mineral corticosteroids induce renal absorption of sodium and decrease sodium excretion in the saliva and sweat (Eisenmenger et al., 1950; Bongiovanni and Eisenmenger, 1951). Moreover, the concomitant increase of potassium excretion also points to adrenal control.

* This problem is discussed in this section because of the influence of th[illegible] on water and sodium absorption by the kidney.

involvement was in the proximal convoluted tubules but other areas were also involved There was no correlation between the glomerular and tubular changes

Correlation of these morphological changes with jaundice and the injurious effect of bile acids on the kidney is not borne out by this study (Table 68) since some of the anicteric

TABLE 68

Relationship of Jaundice to Tubular Degeneration

	Cases	Grade of Tubular Degeneration 1	2	3	4
Cirrhosis with Jaundice	9	0	1	6	
Cirrhosis without Jaundice	16	3	7	5	1

From Baxter and Ashworth Arch Path 41 470 1946

patients showed the most marked renal changes There did seem to be some correlation between the extent and severity of the renal and hepatic changes Therefore the possibility exists of a toxic substance which is elaborated as a result of the hepatic damage injuring the kidney or the etiologic factor responsible for the cirrhosis is also responsible for the renal lesion Accessory factors such as shock in the cases with hemorrhage must be considered

Glomerulonephritis in Hepatic Disease

The increased susceptibility of patients with liver disease to various types of infections makes them an easier prey for the development of glomerulonephritis Patek and associates have recently supplied data which confirms this suspicion Of 100 patients with cirrhosis 14 had evidence of concomitant glomerulonephritis This incidence of 14% may actually be higher since the autopsy incidence of glomerulonephritis was 11.7% The cirrhoses in patients with renal disease included 10 cases of Laennec cirrhosis three of post necrotic cirrhosis one mixed type There was no correlation between the severity of the cirrhosis and nephritis but the higher incidence in the autopsied cases may suggest that incidences of renal disease increases with the severity of the hepatic disease The hepatic disease preceded the nephritis by months or years The glomerulonephritis in the autopsied group of cases was classified as chronic in four subacute in 2 and acute in one and all were classified as the intercapillary type None resembled the lesion described by Baxter and Ashworth The development of exacerbations of the glomerulonephritis were related to respiratory or other infection Hepatic failure was precipitated by the intercurrent nephritis It is interesting to note that five of the 14 patients with nephritis had a normal and one a subnormal blood pressure of 90/40 This may be related to the vasodilating mechanism to be described subsequently (p 465)

Hepatic Injury in Renal Disease

One might expect that the hypoalbuminemia and severe urinary protein loss in some forms of nephritis would have an untoward effect on the liver Boyd studied 71 patients with various types of nephritis including those with hypoalbuminemia and found no disturbance in any of the liver function tests The hypoalbuminemia of nephrosis is characterized by a normal serum cholinesterase while that of hepatic disease is characterized by a low value of this enzyme

HEPATORENAL SYNDROME

The term hepatorenal syndrome originated with our surgical colleagues in reference to the so called liver deaths following cholecystectomy Heyd classified the hepatorenal syndrome into three groups (1) postoperative hyperpyrexia coma and death in 18 to 36 hours (2) prolonged obstructive jaundice and prolonged history of hepatobiliary disease followed by oliguria stupor coma and death four to seven days postoperatively (3) hyperpyrexia absent oliguria azotemia and renal failure predominated It seems obvious that no specific or uniform process was involved in these three groups A variety of factors and circumstances conspired to create these shocking results following cholecystectomy In the cases with hyperpyrexia overwhelming infection was probably the crucial factor in the pre antibiotics era It should be conceded that severe hepatic necrosis may be accompanied by hyperpyrexia

In group 2 the prolonged jaundice and hepatobiliary disease was undoubtedly ac

companied by considerable degrees of liver damage to this was added the trauma and shock of the operation as well as the toxic effects of the anesthetic agent The pre and postoperative care of the patient was not directed at correcting the liver damage The result was a rapidly progressive liver failure

The third group was probably primarily renal failure either due to a preexisting renal *lesion decompensated by the shock of the* operation or a lower nephron syndrome So while the hepatorenal syndrome of the 1940s is a conglomeration of unrelated entities the combination of renal and hepatic disease is not a mere coincidence and can be divided into various categories

1. Mild disturbance of renal function in hepatic disease especially when accompanied by ascites
2. Renal dysfunction and albuminuria in acute hepatitis
3. Increased incidence of glomerulonephritis in cirrhosis
4. Tubular and glomerular changes in cirrhosis
5. Specific infections involving the kidney *and liver (Weil s Yellow fever)*
6. Choline deficiency involving liver and kidney
7. Toxins producing renal and hepatic injury
8. Severe traumatic injury of liver followed by azotemia
9. Hepatobiliary disease followed by azotemia

Carbon tetrachloride intoxication is illustrative of the combined hepatic and renal damage The renal damage may dominate the clinical picture (p 161) although the reverse is usually true The renal damage is usually of the type referred to as the lower nephron syndrome The severe renal damage following traumatic injury of the liver and death from hepatic and renal failure has been described (Helwig Schutz and Orr) While a specific hepatic toxin was looked for and postulated the development of a lower nephron syndrome from severe crushing injuries to other parts of the body (crush syndrome) puts the renal lesion following hepatic trauma into the same category and refutes the theory of a specific hepatogenous toxin The severity of renal involvement and azotemia did not parallel the degree of hepatic necrosis This is another reason why a specific hepatic toxin cannot be postulated

Now the final group we have to consider is the development of severe renal disease and azotemia precipitously after severe liver disease This sequence of events has occurred frequently enough that the conclusion seems warranted that the liver disease is the cause of the renal disease in these instances There are two distinct types of hepatobiliary disease which may show such sequence of events (1) prolonged obstruction of extrahepatic bile ducts and (2) severe parenchymatous hepatic disease

The following case illustrates the sequence of events that one sees occasionally in post hepatic (obstructive) jaundice A 66 year-old man was found to have jaundice on examination for other reasons The jaundice was painless and unobserved by the patient but clay colored stools were present for ten days prior to the examination A urea nitrogen prior to the onset of jaundice was 19 mg % While the patient was being studied for the exact etiology *of the icterus he became stuperous oliguric* and mild albuminuria appeared Urea nitrogen increased to 130 mg creatinine 5 2 mg % and he expired three weeks after the appearance of *jaundice in a state resembling uremia* The autopsy showed obstruction of common duct by a calculus (Fig 17) early biliary cirrhosis and cholemic (bile) nephrosis The nephrosis was characterized by tubular degeneration and necrosis staining of tubular epithelium *with* bile and obstruction of tubules with bile and hyaline casts (Fig 83) the glomeruli were free of involvement

The conclusion seems warranted that the biliary disease was in some way responsible for the renal lesion The hyperbilirubinemia and the bile staining of the tubular epithelium has led to the assumption that the retained bile is responsible for the renal lesion *hence* the name bile nephrosis or cholemic nephrosis

What fraction of the bile is responsible for the renal lesion? Stewart and Cantarow succeeded in producing renal tubular damage in dogs and cats by injection of sodium dehydro

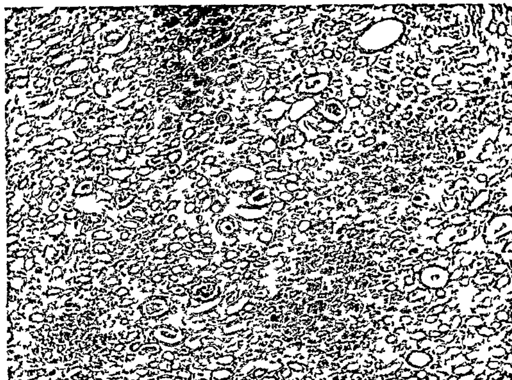


Fig 83 B le n phro Se on of kidne (X oo how ng tubu e p ugged w h b e dege a n of b a ep h l um a o h m h ge a d conge on

cl late n tlerape t c d e Ih s co ld l e produced n an n al w th and w tho t b l ary ol truct on Th the ncongruou part of tl e b er at n f exce e an nts of l le ac d pr duce renal nj ry when excreted b the k l eys b l a y tr s ho l l by d ert ng tl e b tan e fron excret n l the l ver to tl e k dne s ncrea e dan age to the latter organ The ncre ed acc n lat n of b le alt n tl e l ood of pa ent v th po tl epat c ja n l ce and the r excret n l tl e k ines c l l rr t te tl e re al tul ules and lamage then howe e ne tl er an nal exper nents n r cl n cal exper e ce upl ld the nd ct nent of l le salts r ac l as tl e ole cau e ot k lne la age

Ch lem c nep hro occurs n hepat c j un l ce a well l at ent w tl se ere hepat necr n t al ptl le el p a ked ol gu a all nur a e l ndrur a an l azotem w tl a ter nal p ct re f re a Even pat ents w th n derate hepat t n ay show alt u n n tl e rine I cke m l ela cal stu l et the path logy f fatal ep de n c l epat t found les ons n most k lne typ cal of ch le n c nephros N w n eve l ver ne ro the ynthe t b le alts decrea e l t tl e van l ng po nt and hence the k lnes woul l not l e l dened th exces ve excret on f the e l tance B l rul n h we er s ex crete l n large an unt and the l le ta ned t bular ep thel makes one w n ler about t t x c effect n the tul ules Tl e renal nj ry cannot l e attr l te l ent rel t l le r any of t e nst tuents There n l rect relat on l p l etween the degree and durat o f ja n l ce an l the renal lan age Ev lence of renal rr tat n n ay antedate tl e appearance of ja nd ce or may occ r in the al ence of jaund ce B l r b nur a n ay appear bef re tl e en m b l r l n (pron pt react ng type) s ele vated an l th pl en n enon ha been attr b-uted to renal rr tat n Az tem a loes not parallel the hyperl l rub nem a or it durat n In ntant w th congen tal atres a cf the b le lucts tul ular changes occur l ut ol gu a is

companied by considerable degrees of liver damage to this was added the trauma and shock of the operation as well as the toxic effects of the anesthetic agent The pre and postoperative care of the patient was not directed at correcting the liver damage The result was a rapidly progressive liver failure

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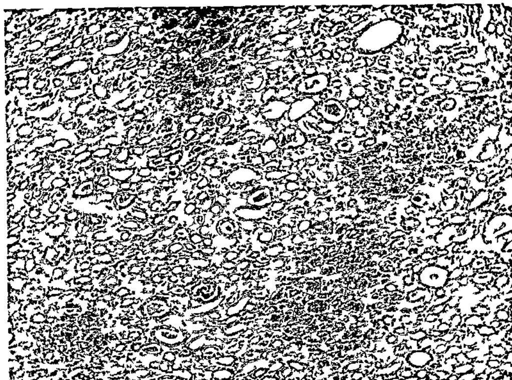
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F g 8 B l neph Sec on o k d ey (X oo) show ng ubu e pl gg d w h b e deg e a n of tubu a ep h l m a a of h m hage nd cong on

cholate n the apeut c doses Th s could be produced n an n al th and w thout b l ary obstruct on Th s the ncongr ou pa t of the observat on t excess ve amounts of b le ac d p oduce renal njur when excreted by the k dneys b l a y stas s hould by d vert ng the ub tance from excret on by the l ver to the k dney ncrea e damage to tl e latter organ The ncreased accumulat on of b le salts n the bloo l of pa ents w th posthepat c jaund ce and the r excret on by the k dneys could rr tate the ren l t bules and da nage them howe er ne ther an mal exper me ts nor cl n cal exper ence pholds the nd ctment of b le salts o ac d a the sole cau e of k dney dam ge

Cholem c nephro s occu s n hepat c jaun l ce a well Pat ents w tl severe hepat c necro s may ab uptl develop marked ol gur a albun nur a cyl ndru r a and azotem a w th a ter n nal p cture of u em a E en pat ents vitl noderate hepat t s i ay show albu n n n the i r ne l ucke n h clas cal study of the pathology of fatal ep dem hepat t found les ons n most k dneys typ cal of holem c nephro s Now n se ere l ver necros the synthes of b le salts decrea ed to tl e van sh ng po nt and l ence the k dney would not be burdened w th excess ve excret on of these substance B l rub n howe er s ex reted n large an ounts and the b le sta ned tubular ep thel um makes one wonder about t tox c effect on the tubul s The renal njury cannot be attr buted ent rely to b le or any of ts const tuents Th re no d rect relat on sh p between the degree and durat on of jaund ce and the renal da nage Ev dence of renal rr tat on n ay antedate the appearance of jaund ce or n ay occ r in the absence of jaun l ce B l rub nur a may appear before the ser m b l rub n (prompt react ng type) is ele vated and th phenomenon has been attr b uted to renal rr tat on Azotem a doe not parallel the hyperb l rub nem a or it durat on In nfants w th congen tal atres a of the b le ducts tubular changes occur but ol guria is

absent The case cited above had a common duct obstruction for about three weeks when marked azotemia appeared other patients can go on with complete biliary obstruction for many months without marked renal damage or azotemia

It seems obvious that the pathogenesis of cholemic nephrosis has not been clearly elucidated There must be other factors besides bile to account for this type of renal injury The various causative factors can be grouped under three headings (1) hepatic (2) renal and (3) extra hepatorenal The similarity between the renal lesion after trauma to liver and the crush syndrome in general has been pointed out The multiplicity of conditions that may eventuate in lower nephron nephrosis is common knowledge Bile nephrosis has clinical and pathological features which fit admirably into this category of renal lesion While the exact mechanism of production of lower nephron nephrosis remains a problem for future investigation a circulatory disturbance or anoxia of the kidney is the most reasonable postulate

In view of the recent investigation into the vastropic principles (see below) originating in the liver and kidney involvement or injury of these organs can be conceived as producing profound circulatory disturbances While the objection that has been raised to an unknown toxin or substance of hepatic origin as the cause of the renal lesions in hepatic trauma may be valid yet it is conceivable that hepatic injuries as well as trauma to other parts of the body may act through the liver in producing the lower nephron syndrome In post hepatic jaundice the liver may become secondarily involved and the hepatocellular injury rather than the hyperbilirubinemia may be responsible for the renal damage This may account for the lack of correlation between the degree of jaundice and the renal damage The patient cited above showed evidence of hepatocellular damage as revealed by the elevated thymol turbidity (7 4 u) 4+ cephalin cholesterol flocculation a total cholesterol of 90 and esters of 41 % The rapidity with which some patients develop azotemia after common duct obstruction may depend in part on the rapidity with which hepatocellular damage occurs Antecedent hepatic injury may be present in some of these patients

One must not overlook renal damage which may have preceded the development of the hepatorenal syndrome In an individual over 60 years of age circulatory abnormalities producing some degree of renal ischemia may be expected The presence of urinary retention may also make the kidney more vulnerable to the final physiologic breakdown

Finally a non hepatic and non renal factor may produce injury of both organs Many known toxins chemical and bacterial are known to do this (Table 67) Bacterial toxins have been incriminated as responsible for renal damage since this syndrome can occur in hepato biliary suppurative processes (Bartlett) Any factor which interferes with circulation and oxygenation may be important in the pathogenesis of this syndrome Thus arteriosclerosis atherosclerosis and cardiac failure as well as severe anoxia from other causes may contribute Shock and dehydration may by reducing renal blood flow set the stage for renal involvement in liver disease

Summary

The hepatorenal syndrome is a conglomeration of poorly defined clinical entities however renal involvement of various types in hepatic disease has been demonstrated in animal experiments postmortem and clinical material While glomerular involvement has been mentioned tubular degeneration and necrosis is the common lesion Cholemic or bile nephrosis belongs to and is a particular form of lower nephron nephrosis Bile salts and pigments may irritate the renal tubules but probably play only a contributory role Hepatic and renal damage of varying degree and duration may precede its development An unknown factor or the vasotropic principles from the liver and kidney (see page 485) may play the crucial role Anything that interferes with circulation (renal blood flow) and oxygen exchange will serve as important contributory causes

Treatment

The treatment of the hepatorenal syndrome is equivalent to treating a patient for

hepatic and renal failure at the same time The treatment of hepatic coma without azotemia is described on page 577 Azotemia complicates the therapeutic problem Because of the necessity of combating anoxia and renal ischemia blood transfusions are indicated in spite of azotemia especially if the serum proteins and hemoglobin are depressed Fresh blood transfusions are better than stored blood because they supply prothrombin which may be depressed Fluids as well as blood must be administered slowly and carefully because if the urinary output is very low pulmonary edema may be produced by fluids which the kidney cannot dispose of Glucose is needed not only for its caloric value but also for the liver Glucose may have to be administered in distilled water because of hypernatremia Hypocalcemia may be counteracted by intravenous calcium gluconate Sodium bicarbonate may be given in small doses intravenously for marked acidosis Vitamin supplements should be given as for liver disease

Special forms of treatment can be utilized for the azotemia but require special equipment or trained personnel Among these should be mentioned peritoneal and intestinal lavage and the use of an artificial kidney Snapper and Schaeffer successfully used exsanguino transfusions in two patients with hepatitis and uremia The complete replacement of the blood they postulated may have resulted in the elimination of some toxin however they also considered the sodium citrate and the normal blood protein as responsible for the beneficial effect

Prognosis of the hepatorenal syndrome is poor indeed and yet some patients recover even with the supportive and conservative measures described above

The Role of Hepatorenal Factors in Shock Hypertension and Edema

The fundamental and important studies of Shorr and his associate on circulatory homeostasis have been summarized in their papers cited in the bibliography Their investigations led to the conclusions that the circulation in the capillary bed connecting the terminal arteriole (metarteriole) with the venous side of the circulation is under humoral control These substances are the vasoexcitor (VEM) factor elaborated by the kidneys and vasodepressor (VDM) factor elaborated by the liver These factors act by increasing (VEM) or decreasing (VDM) the reactivity of the terminal arterioles and precapillaries to epinephrine Normally VEM and VDM are so balanced that the capillary circulation is maintained at the optimum level

When VEM predominates ischemia results from increased vascular tone while predominance of VDM results in congestion from decreased vascular tone The fine balance for optimal physiologic needs is maintained not only by control of production but also by inactivation of these factors VDM is elaborated chiefly in the liver and to a lesser extent in the spleen and skeletal muscles Oxidative inactivation of VDM is accomplished only by the liver VEM is elaborated only in the renal cortex and is inactivated almost entirely by the kidney and only to slight degree by the liver The VDM inactivating capacity of the liver is markedly impaired by ischemia and this is a primary factor in disturbing the equilibrium between these two substances with the resultant loss of circulatory homeostasis

Shock

The chain of events encountered in shock are as follows The initial blood loss results in renal ischemia sufficient to put in motion an anaerobic process which leads to elaboration of VEM The increased circulating vasoconstrictor principle maintains adequate blood flow in spite of reduced circulating blood volume During this hyperreactive phase of shock the animal can recover with adequate blood transfusions

If this phase of shock goes untreated for a long time or the hypotension is prolonged and profound renal blood flow is impaired to the point where VEM elaboration is halted Liver ischemia initiates an anaerobic process in this organ which leads to excessive production of VDM Moreover hepatic inactivation of VDM is halted the vasodilator substance causes further vascular collapse the hyporeactor or irreversible stage of shock is reached At this point blood transfusions no longer can save the individual (Fig 84) The susceptibility of

experimental animals and patients with liver disease to profound and irreversible shock may depend on their inability to inactivate VDM

Hypertension

It can be surmised from the action of the substances described above that the maintenance of the blood pressure in a normal animal may depend on an equilibrium between VDM and VEM Disturbances in one or the other organ (liver or kidney) may result in predominance in one of these substances which may lead to hypo or hypertension Anoxia of the liver and kidney is a stimulus for the elaboration of these factors This assumption was verified in the dog by clamp compression of one of the renal arteries This created renal anoxia, and VEM was recovered from the blood during the rise in blood pressure When the blood pressure reached a plateau VEM was no longer recoverable presumably because the increased blood pressure abolished the renal ischemia Moreover, the metabolism of the partially clamped kidney is changed so profoundly that tissue slices from such kidney can produce VEM aerobically, whereas non ischemic kidney slices produce VEM only anaerobically The ischemic kidney slices also lose their capacity for inactivation of VEM

It was further noted that the apparent absence of VEM in the serum of chronic hypertensive dogs was due to its neutralization by

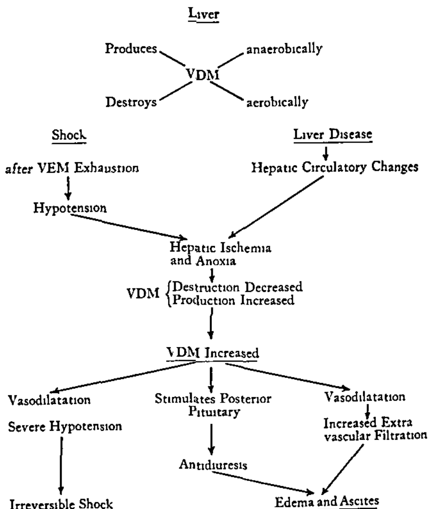


Fig 84 Schematic presentation of the role of VDM and VEM in the production of irreversible shock edema and ascites

increased amounts of VDM The blood pressure was stabilized at a higher level by increased hepatic production of the vasodilator substance VDM Similar observations were made in patients with chronic hypertension that is the increased circulating VEM was neutralized by an increased amount of VDM Blood from normal individuals showed neither VEM or VDM that is gave a neutral reaction These observations indicate that in experimental hypertension as well as human hypertension the vasoexcitor (VEM) substance from the kidney and vasodepressor (VDM) substance from the liver play a role in hypertension

The renal production of VEM seems to depend on intact adrenals Kidney slices from adrenalectomized rats rabbits and dogs were unable to produce VEM anaerobically Desoxycorticosterone and NaCl administration to these animals resulted in a recovery of this function

It becomes clear from the above observations that the maintenance of a normal blood pressure requires normally functioning kidneys and liver In derangements of the liver VDM inactivation becomes impaired resulting in greater accumulation in the blood stream and drop in blood pressure This may explain the hypotension and other circulatory derangements in patients with liver disease

Implications of VEM and VDM in Edema and Ascites Formation

When the capillary bed is in a hyper reactive state that is vasomotion is increased under the influence of excessive amounts of VEM there is reduced blood flow through the capillaries favoring inward filtration This creates dehydration and hemodilution Under the influence of excessive amounts of VDM sphincteric relaxation and hyporeactivity results in a wide open capillary bed filled with blood The increased hydrostatic pressure created favors outward filtration and edema formation

In patients with congestive heart failure the anoxia stimulates the anaerobic mechanism for elaboration of VEM and VDM The renal and hepatic veins of patients in congestive heart failure were found to contain VEM and VDM respectively The lack of equilibrium between these substances in patients with heart failure may account in part for change in blood pressure and edema formation

The derangement of these vasotropic principles in cirrhosis and liver injury in general is of fundamental importance The intolerance to shock of subject with deranged liver function has been mentioned Animals with dietary liver injury were found to have considerable VDM in their livers and in the circulation and their mesenteric blood vessel were non reactive to adrenalin like animals in irreversible shock The kidneys apparently had lost their ability to form VEM and thus the animal was deprived of the humoral mechanism to protect it from shock This vasotropic derangement in liver disease may tend to promote the renal failure (hepato renal syndrome) which as was mentioned may be induced by renal anoxia and be related to lower nephron nephrosis which is a sequel of certain types of shock

The renal VEM mechanism curiously enough is dependent on adequate protein intake Another factor necessary for normal VEM formation is desoxycorticosterone (DOCA) or the adrenal cortex Methionine and DOCA administration may revive the VEM synthesis in rats with nutritional cirrhosis

Studies in patient with cirrhosis amplify and clarify this very interesting problem Patients with decompensated cirrhosis showing edema and ascite showed the presence of VDM in the blood and edema fluid Patients with cirrhosis without ascites or edema showed no VDM and VEM was absent in both Moreover patients with ascites and edema of other origin (nephrosis) also showed finding similar to those in decompensated cirrhosis This implicates VDM as an important factor in the production of various types of edema

The antidiuretic effect of VDM has been demonstrated in animals Injection of VDM ferritin or apoferritin with which VDM is identified into rabbits and dogs leads to profound antidiuresis It is postulated that elevation of VDM in the blood of cirrhotic individuals stimulate the posterior pituitary to secrete antidiuretic hormone and this in turn produces the antidiuresis (Fig 84)

in 53.2% of patients with rheumatic heart disease and in 35.5% classified as hypertensive heart disease and in 9.7% classified as arteriosclerotic heart disease. The type of valvular lesion most likely to lead to congestive cirrhosis is tricuspid stenosis and next in frequency is tricuspid insufficiency. The valvular lesions are usually multiple.

The overall incidence of hepatic involvement in congestive failure varies widely among different observers. This wide variation is due largely to the severity of the lesion that they classify under this heading. Obviously when minimal fibrosis in a patient with heart failure is classified as cardiac cirrhosis the incidence is unduly high. Thus Katzin and associates found increased hepatic fibrosis in 95 or 33% of 286 cases with decompensation while Garvin found cardiac cirrhosis in only 4.4% of 790 autopsied patients with heart diseases. In Kotin and Hall's series the incidence of cardiac cirrhosis was about 10% or 6[illegible] among 605 patients with decompensation. The high figure of 33% cited above has significance in as much as it suggests that patients with chronic heart failure do show a high incidence of hepatic fibrosis as compared with 1714 cases without congestive failure who had a 12% incidence of hepatic fibrosis.

There are other factors which influence the extent of fibrosis. One of these factors is the duration of congestive failure. Thus most surveys are in agreement that the longer and more frequent episodes of failure predicate more extensive hepatic injury. Kotin and Hall, however, found recurrent episodes of decompensation more effective in producing hepatic injury than single episodes. *The initial bout of* congestive failure may occur between 3 months and 30 years before the appearance of liver changes. The apparent discrepancy between the effectiveness of the two time factors, duration and recurrent attacks of congestive failure in producing hepatic fibrosis is really one of perspective and may be reduced to a common denominator. Thus to take two extremes, a patient with a history of heart failure dating back 30 years and another patient with a history dating back 4 months, the one with the longer history may conceivably have had only [illegible] bouts of failure while the one with a 4 months history may have had eight bouts of failure. It seems that the total duration of the circulatory impairment of the liver as well as the degree of this impairment may be crucial in the development of cirrhosis.

Nutrition, as was mentioned before, may play a role in the production of this hepatic lesion. There are few studies making this correlation. Felder and coworkers found evidence of malnutrition in 54% of their patients and as expected malnutrition paralleled the duration and severity of the cardiac disease.

Toxins have not been proven to contribute to the development of cardiac cirrhosis although a liver with impaired circulation would be more susceptible to injury by toxins. No correlation has been found between the administration of mercurial diuretics and the development of this type of cirrhosis (Kotin and Hall).

The age of patients with cardiac cirrhosis varies widely between childhood and senility, 10 to 85 years. The average age in the post mortem studies is about 50 years. Since rheumatic heart disease contributes a disproportionate number of patients with cardiac cirrhosis and this type of heart disease is more common in younger individuals, a preponderance of this hepatic lesion may be expected in the younger age group.

Sex does not appear to be of etiologic importance and the distribution between the sexes appears to be equal.

Summary—Etiology

A. Types of Heart Disease
   1. **Constrictive Pericarditis**
   2. **Rheumatic Heart Disease**
      a. **Tricuspid stenosis**
      b. **Tricuspid insufficiency**
      c. **Other valvular lesions**
   3. **Arteriosclerotic and Hypertensive Heart Disease**

B. **Time Factors in Congestive Failure Influencing Hepatic Injury**
   1. **Recurrent Attacks**
   2. **Duration of Failure**

C. **Other Factors**
   1. **Nutritional Impairment of Chronic Illness**

2. **Toxins Unrelated to Cardiac Disease**
3. **Age 10 to 85 Years—Most Common 4th and 5th Decade**
4. **Sex Equal Distribution**

Pathogenesis

There are two major factors resulting from disturbed circulatory dynamics which are responsible for the development of the hepatic lesion One of these is mechanical the other chemical The mechanical factor is congestion or stasis or as Moschcowitz insists central portal hypertension The chemical factor is anoxia The relative importance of these two factors in a given case of cardiac cirrhosis in general is difficult to appraise This differentation is more of academic than practical importance since the two defects usually parallel each other

The effect of the congestion of heart failure on the liver was observed as the nutmeg liver over 100 years ago (Kiernan 1833) The effect of congestion on the liver has also been demonstrated experimentally by partial obstruction of the vena cava above the hepatic veins There is no doubt about the presence of venous stasis but Moschcowitz argues that venous stasis is not synonymous with increased venous pressure and the latte is the mechanical factor responsible for the liver injury During compensation the venous pressure returns to normal while congestion may persist He regards the marked sclerosis of the hepatic veins in constrictive pericarditis as the result of the increased pressure and the dilatation of the central vein and its tributaries as a result of the flow of blood against increased pressure The hepatic capillary and venous sclerosis are also attributed to the increased venous pressure

Moschcowitz also explains the development of new capillaries and anastomosis between the portal and central and hepatic veins on the basis of venous hypertension in accordance with the law of Thoma According to Thoma s law the formation of new capillaries depends on the difference between intracapillary pressure and the pressure in the surrounding tissue spaces If the intracapillary pressure increases markedly new capillary formation is stimulated According to these postulates the thickness of a vessel wall increases with increasing intravascular pressure thus explaining the *phlebosclerosis*

Anoxia the other factor accountable for the liver damage in congestive failure is a well known cause of centrolobular hepatic necrosis The centrolobular necrosis is easily explainable on the basis of diminishing oxygen supply as the center of the lobule is reached Sinc the blood flows from the periphery of the lobule toward the center periportal areas may remain oxygenated even when the oxygen saturation is reduced Oxygen saturation in the hepatic vein was found to be very low by Evans and coworkers and the arterio venous oxygen difference was increased in patients with congestive failure The anoxia is dependent on the reduced cardiac output increased circulation time and decreased oxygen saturation The latter however may be only slightly reduced In addition the circulatory disturbance results in a greater dependence of the liver on the portal venous blood supply which is markedly slowed and rendered inefficient by the venous congestion and hypertension The centrolobular anoxia finally reaches a point that can no longer sustain the viability of the cells

Pathology

Grossly the liver is usually smaller than normal The surface may be smooth finely granular or nodular The organ is firmer than normal The cut surface shows the purplish mottling of passive congestion

The microscopic morphologic changes begin and are most marked around the central vein At first the sinusoids especially in the center of the lobule become dilated and markedly engorged with blood This leads to capillary sclerosis and compression of the hepatic cell cords Centrilobular necrosis and atrophy occurs followed by condensation of reticulum Wallach and Popper have pointed out that there are no cell remnants in this type of necrosis Kotin and Hall found more atrophy than necrosis in their material There is a limited invasion of lymphocytes plasma cells and polymorphonuclear leucocytes in these areas

If normal circulation is reestablished after a short period of time the centrolobular cells regenerate and normal architecture is restored If the congestion and anoxia continue the necrosis spreads from the central area peripherally The reticulum tissue is not only condensed but shows active proliferation



Fig 85 Congestive cirrh is Needle b psy f l v r (X oo) r ned w th Mall rs fibro s t s e sta show g sclero s of ce tr l ve n increa d cent olobul r fib o s t ue rgorgem nt of s n soids Patien age 54 mitral t nos s and in fficı ncy tricusp d ns ffici n y r peated pisodes of cong st fa lure for six y a s

As the process becomes more marked the strands of fibrous tissue reach out to join those arising from adjacent lobules (Fig 85) While the periportal areas are unaffected early the advanced cases with fibrous strands reaching across the lobular bounda ries finally entangle the portal spaces as well giving a final picture indistinguishable from portal cir hosis These step by step changes have been demon strated graphically by needl biopsies of the liver (Sherlock)

Although Katzin and his associates found in creased per portal fibrosis in 5% of their patients with congestive failure as compared with 9% in their n n cardiac cases it is difficult to attribute the portal fibrosis to purely circulatory changes As was stated above in advanced cases f cardiac cir rhosis portal cirrhosis may be simulated Nutritional factors may conceivably play a role in the production of portal fibrosis It seems that the circulatory de rangement of the extent found in congestive failure would impair the resistance of the hepatic cells to other noxious agents The decreased resistance of anoxic animals to CCl poisoning has been demon strated Exposure of an individual with repeated episodes of cardiac failure to malnutrition alcohol and other cirrhotogenic agents should lead more quickly and certainly to cirrhosis In order to refut that congestion of the liver predisposes to portal cirrhosis one must demonstrate that these indi viduals are singularly free from contact with the other etiologic agents of portal cirrhosis

The central veins are dilated and their walls are thickened and sclerosed The hepatic veins show similar changes The thickening and scleros s also involves the capillaries Moschcowitz emphasizes the increase of vascular septa the multipl cation f capillaries and the formation of shunts between portal and hepatic vein radicals These shunts are formed between various orders of hepatic veins and the bridging is done by newly f rmed capillaries or venules in the proliferated reticulum and fibrous tissue This vascular and fibrous tissu proliferat on results in the loss of identity of the central vein The portal triad may assume a central positi n or the newly formed capillaries and venules may represent the new central vein

Multipl cation of bile canaliculi and ducts occur but is not a prominent feature Bile thrombi and intracellular and extracellular pigment has been mentioned especially in the biopsy material Nodu lar regeneration of liver cells has also been noted

Glisson s capsule may be thickened This is espe

cially marked in constrictive pericarditis in which the fibrous thickening of the capsule assumes the so called sugar icing appearance (Zuckerguss) In tri cuspid lesions the capsule of the liver is also fre quently thickened but not to the same extent as in constrictive pericarditis

Peliosis hepatis is a term used for a rare condition in which the liver shows diffuse angiomatous changes This is also referred to as Telangiectasia hepatis disseminata angiomatosis hepatis and Leberblutung Although the etiologic factors re sponsible for this condition have not been clearly established it is thought to be the result of long continued passive congestion Hamilton and Lubitz *recently reported three additional cases*

The spleen unlike the liver is almost invariably enlarged in cardiac cirrhosis and shows the changes of congestive splenomegaly These changes are not as marked as in portal or in splenic vein occlusion

Other pathologic findings of importance are those involving the heart and circulatory system and need not be elaborated upon here The etiologic cardiac lesions have been mentioned Ascites is a frequent finding in the advanced cases of congestive cirrhosis This complication will be discussed in more detail under clinical features

Summary—Pathogenesis

Depends on Two Factors

1 Mechanical

Increased Venous Pressure

2 Chemical

Anoxia Most Marked in Hepatic Vein

Both of These Factors are More Pronounced in

The Center of the Lobule around Central Vein therefore

Changes are Centrolobular in Origin

Summary—Pathology

Liver

Gross

Liver smaller than normal

Firm

Smooth granular or nodular

Purplish mottling

Microscopic

Central vein dilated

Sinusoidal congestion—centrally

Capillary and venous sclerosis

Sinusoidal compression

Centrilobular atrophy and *necrosis*

Reticulum condensation and proliferation

Fibrous septa originate centrally but eventually reach the portal areas resulting in

Disturbance of relationship between central vein and portal spaces

Capillary proliferation results in hepatic and portal vein anastomosis

Multiplication of bile duct

Nodular regeneration

Glisson s Capsule

thickened—especially in constrictive pericarditis (Zuckerguss)

Spleen

Congestive splenomegaly

Clinical Features

The foregoing discussion implies that a clinician following a patient with congestive heart failure should be on the lookout for the development of congestive cirrhosis if the failure is recurrent and has been present for 6 months or more Only advanced cases of hepatic fibrosis are of importance as far as the clinical course and treatment are concerned and even the advanced cases may be difficult to distinguish from uncomplicated heart failure with passive congestion of the liver

The clinical features that one should look for in detecting cardiac cirrhosis are

1 changes in the liver
2 splenomegaly
3 ascites and
4 jaundice

The *liver* in failure of the right ventricle or both ventricles is enlarged and tender The weight of the liver in cardiac cirrhosis is usually less than normal but loss of blood from the congested liver may account for this sinc the liver invariably appears enlarged clinically in congestive failure Parenchymal cell necrosis and contraction of fibrous tissue may result in some shrinkage of the liver as cardiac cirrhosis develops Therefore a decrease in size of the liver in spite of continued congestive failure or fixation of liver size with clearing of failure would suggest the development of fibrosis Increase in consistency of the liver on palpation would likewise suggest development of cirrhosis The fine irregularity of even the fully developed cardiac cirrhosis can hardly be pal

pated through the abdominal wall With the development of cirrhosis the tenderness may decrease or disappear

Splenomegaly is almost a constant feature of cardiac cirrhosis When the spleen becomes enlarged while the liver shrinks cirrhosis is likely to be present

Ascites is another frequent finding in cardiac cirrhosis It may be absent however in this type of cirrhosis and its presence is not an assurance of cirrhosis If ascites were extremely rare in congestive heart failure without cirrhosis it would be an extremely helpful sign In constrictive pericarditis massive ascites precedes the development of cirrhosis In other types of heart disease clinically troublesome ascites is not common When massive ascites requiring paracentesis develops it is likely to be due to associated liver disease

Ascites was present in all patients with cirrhosis studied by Boland and Willius but 86 6% of the entire series of congestive failure showed its presence The degree of ascites however is not indicated in the two groups The group studied by Kazin and associates showed marked ascites only in the cirrhotic group Since some of the factors involved in salt and water retention in heart failure and liver failure are similar (p 500) it can be readily understood that ascites would not be a monopoly of either disease The response to salt restriction may be favorable in both diseases It may be worth re emphasizing that massive ascites points to hepatic complication but cardiac cirrhosis may exist in the absence of ascites

The presence of jaundice immediately turns our attention to the liver Frank clinical jaundice is uncommon in cardiac cirrhosis and may occur in heart disease with an intact liver However hyperbilirubinemia is frequently present and intense jaundice is usually accompanied by widespread central necrosis Since mild hyperbilirubinemia is frequently found in heart failure in general it is not very helpful in detecting the presence of cirrhosis but it is helpful when added to other clinical findings

The pathogenesis of jaundice in heart failure may be attributed to hepatic and prehepatic factors However it seems that hepatic factors are very important even when no definite cirrhosis exists The increased production of bilirubin from hemolysis of blood in various sites but especially in pulmonary infarcts is important in the genesis of jaundice The accumulation of cells containing iron pigment in various tissues in heart failure favors this hypothesis Increased urinary urobilinogen excretion is also in conformance with this However jaundice may occur in the absence of pulmonary infarcts Even when no other cause for jaundice can be detected and the hepatic histology appears normal the inability of the liver to excrete a slightly increased amount of bilirubin indicates hepatic dysfunction

The evidence favoring hemolysis as the cause of jaundice in heart failure may be summarized as follows

1 Pulmonary infarction is frequently present in patients with heart disease and jaundice
2 Jaundice may be present with minimal histologic and functional abnormalities of the liver
3 The jaundice may be accompanied by urobilinogenuria but no bilirubinuria
4 Jaundiced patients may show normal bromsulphalein excretion

Jaundice due to hepatocellular damage and in the absence of other etiologic factors does occur Evidence of disturbed liver function as measured by tests other than the serum bilirubin indicates that liver involvement is in large measure responsible for the jaundice The evidence favoring the hepatic rather than extrahepatic (hemolytic) cause of the jaundice in heart disease may be summarized as follows

1 Jaundice occurs in the absence of pulmonary or other infarcts
2 Disturbed liver function is detectable in congestive heart failure
3 Morphological changes in the liver are detectable during life as well as post mortem
4 Anoxia from other causes may produce disturbed liver function and jaundice
5 The slight increase in bilirubin production even in patients with pulmonary

infarcts would not result in jaundice if the liver were functioning normally

6 Bilirubinuria is present

7 Prompt reacting bilirubin in the blood is increased

8 Serum alkaline phosphatase is elevated

Obstruction to the outflow of bile may also play a role in "cardiac" jaundice but the obstruction is intrahepatic and there is no posthepatic jaundice in heart failure The obstruction may be chiefly due to the increased venous pressure compressing the bile canaliculi and finer intrahepatic bile ducts The hepatic vein pressure may exceed the secretory pressure (20–30 cm of water) of the liver The frequency of jaundice in disease of the tricuspid valves suggests that the high hepatic venous pressure may be responsible in its production However jaundice does not occur in all patients with high right auricular pressure and is notably absent in constrictive pericarditis The distortion and compression of bile ducts by hemorrhage proliferating fibrous tissue and regenerating liver cells may contribute to the obstructing process Bile thrombi in the biliary canaliculi are frequently found in patients with deep cardiac jaundice

Opposed to the obstructive nature of cardiac jaundice are

1 The lack of uniform correlation between jaundice and high right auricular pressure

2 Absence of acholic stools There is usually an abundance of bile in the stools

3 Abundance of concentrated bile in the gall bladder and extrahepatic bile ducts post mortem

4 Increase rather than decrease of urobilinogen in the urine

5 Serum alkaline phosphatase is usually not elevated

Laboratory Features (Liver Function Tests)

Attempts to evaluate the functional capacity of the liver in congestive heart failure has been going on for over two decades It is a valuable approach because it can be readily used and followed through the entire course of the illness and at times reveals abnormalities that may be missed by morphological study

Hyperbilirubinemia is much more frequent than clinical jaundice Thus only 5 of 231 patients (2 1 %) had clinical jaundice while 13 of 16 patients (81 %) in the same series showed hyperbilirubinemia (Jolliffe) Increased serum bilirubin in 85 % of patients with cardiac failure was also found by Chavez and coworkers (while no hyperbilirubinemia was found by them in 6 patients without heart failure) Fedder and associates found hyperbilirubinemia in 5 % of determinations and White and coworkers in 43 % (13) of 30 patients with heart failure Evans and associates found hyperbilirubinemia in 26 4 % of their patients, those with pulmonary infarcts were excluded The total bilirubin is usually not high rarely over 6 0 mg % and usually under 2 0 mg %) The more intense hyperbilirubinemias are more likely to be associated with pulmonary infarction and are more common in rheumatic heart disease with mitral stenosis Exceptions to both of these generalizations are abundant Elevation in the prompt direct reacting bilirubin in many of these cases points to the non hemolytic factors involved in its production It is worth emphasizing that hyperbilirubinemia is common in heart failure but very uncommon in heart disease without failure

Serum protein abnormalities are found in a considerable number of patients with heart disease in failure Both depression of the albumin and elevation of the globulin are found The depression of albumin is most logically attributable to hepatic disease unless serious malnutrition is present elevation of globulin in the absence of infection is also most likely due to hepatic dysfunction

Serum albumin values below 3 0 gm % were found in 13 of 30 cases in the New Jersey group and some were below 2 0 gm % Severe hypoalbuminemia may influence the development and perpetuation of edema Hypoalbuminemia and hyperglobulinemia were also noted by Evans and associates This determination is of considerable importance not only in the diagnosis but also in the management of heart disease Herrmann found some correlation between hypoalbuminemia and ascites in heart failure The severe hypoalbuminemias were present in those individuals in whom cirrhosis was present or suspected

Thymol turbidity is frequently elevated in patients with heart disease but this is not confined to patients in failure. Carter and MacLagan found this test positive in 35% and Stollerman in 50% of patients with heart disease with and without failure. Positive tests were especially *high in those with active rheumatic fever. Frost and Dotti also found* elevation of this flocculation test in patients with and without cardiac failure. These tests are usually only weakly positive. Felder and coworkers found the thymol turbidity test slightly elevated in 31%. The cirrhotic group showed an average thymol turbidity of 5.5 units but the variation in all the patients was between 1 and 15 units. White and associates found the thymol turbidity elevated in 4 of 30 patients. Evans and associates found the test abnormal in 36.5% of 105 patients in congestive failure. This test therefore is not useful in detecting liver damage due to heart failure since it is so frequently positive in heart disease without failure; however if one excludes active infection such as rheumatic fever, a positive test may be of limited value.

Cephalin cholesterol flocculation can be appraised similarly to the thymol turbidity test. It is frequently positive in patients with heart *failure but is also positive in rheumatic heart* disease without regard to cardiac efficiency. Kissane and associates found this test positive (above 1+) in 89% of patients with rheumatic heart disease in failure and 69% of those not in failure. Felder and associates found [illegible]% of their patients in failure with cephalin flocculation tests above + and greater flocculation in patients with rheumatic heart disease in failure over three years, those with auricular fibrillation and those showing cirrhosis of malnutrition. One third of the patients studied by White and associates had positive cephalin flocculation tests of 3+ or above. This test was less frequently (4%) positive than the thymol turbidity test in the group studied by Evans and associates.

Alkaline phosphatase of the serum is frequently elevated but not to the level seen in post hepatic jaundice. The elevation of the enzyme suggests hepatic disease and cannot be explained readily on the basis of extrahepatic factors. 46% of the determinations done in Felder's series showed abnormal values. These averaged 5.8 Bodansky units and only 7 of 78 determinations were above 10 units. 7 of 30 patients in another series showed an elevation of this enzyme and only 2 of them *were slightly above 10 units.*

Cholesterol and cholesterol ester deviations are interesting not only from the point of view of hepatic dysfunction but also because of their possible relationship to arteriosclerotic heart disease. In the New York series (Felder et al.) the total cholesterol was depressed (below 150 mg%) in over one third of the determinations but above normal in only 4 of 131. The cholesterol esters were depressed in 33% of tests and were associated with a low total cholesterol. The cholesterol esters were depressed in the malnourished patients and those with histologic evidence of cirrhosis. The series from New Jersey (White et al.) corroborates the above findings; they found the total cholesterol elevated only twice in their group of 30 patients but the esters were depressed in six.

The bromsulphalein excretion test is valuable in detecting hepatic dysfunction in heart failure. It is positive in a high percentage of cases and the degree of dye retention seems to be *well correlated with hepatic cell necrosis (Sherlock).* Patients with heart disease but without heart failure usually show no dye retention but those with heart failure show progressively increasing retention paralleling to a certain extent the degree of failure. The retention of dye may be very severe, that is over 50% at 45 minutes. This test gives the highest number of positive determinations in heart failure approaching 100%. Evans and associates noted a correlation between impaired bromsulfalein clearance and increased venous pressure. Therefore this test can hardly be used by itself to detect cardiac cirrhosis during failure. The reduced hepatic blood flow and altered circulatory dynamics rather than the liver damage per se are largely responsible for the reduced dye clearance. Therefore only the persistence of a positive bromsulphalein test *after* compensation has been restored can be accepted as evidence of liver dysfunction. The return of an abnormal bromsulfalein to a normal level after

compensation has been noted by Blumberg and Schloss It cannot be denied that even during heart failure some of the impaired dye clearance may be due to hepatic cell necrosis which regenerates after the circulation is re stored to normal

Hypoglycemia has been reported in con gestive failure and this may be on the basis of hepatic dysfunction (Mellinkoff and Tumulty)

Needle Liver Biopsy

This procedure has been found useful in studying the evolution of liver injury resulting from congestive heart failure It is superior to post mortem studies in as much as it portrays the changing process during life and does not introduce the artefacts of post mortem changes Since the term cirrhosis refers to certain morphological changes a liver biopsy is the most accurate way of making the diagnosis (Fig 85)

There is some danger from hemorrhage fol lowing a needle biopsy in a patient with a congested liver and high intrahepatic venous pressure However if all the precautions men tioned in Chapter 10 are scrupulously observed the danger is minimized Needle biopsies of liver were performed in 51 patients by Sherlock and in 30 patients by White without untoward outward results I have likewise biopsied pa tients with congestive failure without encoun tering any complications I have found the use of an aspirating needle before inserting the biop sy needle a useful means of avoiding large vascu lar channels One can also minimize the danger by waiting till compensation has been restored and venous pressure reduced before doing the biopsy If considerable fibrosis has developed it will remain after cardiac function has been restored to nearly normal

Sherlock illustrated with biopsy material the centrilobular necrosis leading to fibrosis and finally to complete distortion of architecture as described under pathology One limitation of the needle biopsy in detecting cardiac cirrhosis is that the size of the specimen may render its differentiation from typical portal cirrhosis more difficult The difficulty however is also encountered in post mortem material White and his collaborators made a histologic diagno sis of portal cirrhosis in nearly half of their morphologically abnormal livers in patients with heart failure

The correlation between histological changes as noted on biopsy and the functional changes as studied with liver function tests is not always good Sherlock found good correlation between the degree of hepatic cell necrosis hyper bilirubinemia and bromsulfalein excretion but poor correlation between histology and serum proteins and alkaline phosphatase White and his group found normal liver histology in 17 of their 30 patients but among the seventeen there were many with markedly abnormal tests Venous stasis of the liver should be found in every case with right ventricular failure unless the blood is squeezed out and the architecture changed in the process of obtaining the speci men Fibrosis need not necessarily be present to produce abnormal liver function tests On the other hand abnormal liver function tests may be present in congestive heart failure in the absence of cirrhosis and their abnormality does not necessarily indicate cirrhosis There fore the only positive way of diagnosing cardiac cirrhosis is on morphologic grounds

Clinical Features—Summary

Liver
- **Decreases in size in spite of continued congestive failure**
- **Size of organ remains unchanged in spite of decreased congestive failure**
- **Becomes firmer**
- **Less tender**

Spleen
- **Enlarges especially while liver shrinks**

Ascites
- **Massive resistant to cardiac therapy**

Jaundice
- **Mild in congestive failure without cir rhosis**
- **Moderate in severity points to cirrhosis**
- **Pathogenesis**
  - **Hemolysis of blood in infarcts espe cially pulmonary (see p 493)**
  - **Hepatocellular damage**
    - **See page 493 for points supporting this hypothesis**

Obstruction of bile flow may be present but is
Intrahepatic due to vascular compression of bile ducts

Laboratory Features—Summary

Hyperbilirubinemia
Common but mild in degree
26 to 85% of cases
Serum Proteins
Hypoalbuminemia common
Hyperglobulinemia found but less frequently
Flocculation Tests
Thymol Turbidity
Positive in over 30% of patients with heart disease, with and without failure
In absence of active infection a positive test is significant
Cephalin Cholesterol Flocculation
Positive in about the same frequency and same significance as the thymol turbidity test
Alkaline Phosphatase
Slightly elevated in less than half of patients
Cholesterol and Cholesterol Esters
Both are frequently depressed
Elevated cholesterol rare
Bromsulphalein Excretion Test
Impaired clearance is very common in cardiac failure due to
reduced hepatic blood flow cellular anoxia
Persistence of abnormal clearance suggests cardiac cirrhosis
Liver Biopsy
Most accurate way of making the diagnosis of cardiac cirrhosis
Function test may be abnormal with cirrhosis and
Cardiac cirrhosis may be present with minimal disturbance of tests

Diagnosis the Clinical Detection of Liver Injury in Heart Disease

Heart failure is frequently accompanied by abnormal liver function tests The tests that are frequently abnormal are

1 Serum Bilirubin
2 Bromsulfalein excretion test
3 Flocculation tests

Their abnormality during periods of decompensation does not indicate so called cardiac cirrhosis

The diagnosis of cardiac cirrhosis remains difficult but the following features point to it

1 Repeated episodes of failure with the first episode more than 4 months previously
2 Heart disease accompanied by marked increase in right auricular pressure are more likely to cause it
   a constrictive pericarditis
   b tricuspid stenosis
   c tricuspid insufficiency
   d mitral stenosis
3 Decreasing size of liver with increasing consistency
4 Splenic enlargement when subacute bacterial endocarditis can be ruled out
5 Ascites if massive requiring paracentesi
6 Clinical jaundice in absence of infarcts
7 Decreased serum albumin
8 Marked bromsulfalein retention especially significant if abnormality persists after compensation is restored
9 Liver biopsy showing characteristic histologic changes

Treatment

The treatment of cardiac cirrhosis resolves itself into the treatment of the heart disease and the treatment of the hepatic abnormality Many of the therapeutic procedures have a favorable effect on both conditions It is platitudinous to state that the proper treatment of heart disease and the prevention of heart failure would prevent cardiac cirrhosis Given a patient with chronic heart disease the maintenance of proper nutrition would remove one additional factor that contributes to the development of cirrhosis Exposure to toxins should be scrupulously avoided and the use of alcohol should be limited

When liver disease develops treatment should be directed toward it Some of these procedures are also valuable in the treatment of heart disease Rest is a useful agent in both condition Salt restricted diet is helpful in the

edema and ascites of both conditions High protein diet is helpful in the edema ascites and hypoproteinemia of both conditions Ion exchange resins to reduce salt absorption administered orally are helpful in both conditions Salt free albumin intravenously may be used with caution to reduce edema and ascites in extremely hypoproteinemic patients Vitamin supplements should also be administered For details of these therapeutic procedures see Chapter 77

Prognosis

The prognosis of cardiac cirrhosis is good as far as the hepatic lesion is concerned but death may result from the grave cardiac disease Even in cases of extreme distortion of hepatic architecture from congestive heart failure there are apparently enough functioning hepatic units to take care of vital functions and death from cholemia is rare The serious complications of portal cirrhosis such as esophageal hemorrhage rarely develop in cardiac cirrhosis This is due to the intermittency of the portal hypertension the lower portal vein pressure in this condition as compared with other types of cirrhosis Collateral circulation involving the esophageal plexus does not develop unless some accessory causative factors come into play In such event widespread necrosis may also develop to produce fatal hepatic failure

The important clinical implication of cardiac cirrhosis is the effect that disease of the liver has on the pathologic physiology of the heart

THE ROLE OF THE LIVER IN HEART DISEASE

It would be odd indeed if the liver with its multitudinous functions would play no role in the development and propagation of heart disease The function of the liver in removing foreign substance from the blood extends to removal of bacteria as well In subacute bacterial endocarditis the blood leaving the liver via the hepatic vein contains much fewer organisms than the portal venous blood or the arterial blood entering the liver (Beeson et al) The normally functioning liver may be a bulwark against the development of subacute bacterial endocarditis and undoubtedly plays an important role in filtering the blood and reducing the hematogenous dissemination of bacterial emboli The liver may play a subtler role in protecting the heart against other inflammatory lesions Its role in protein synthesis undoubtedly extends to antibody formation which may aid in preventing the development of rheumatic fever and rheumatic heart disease

The other important form of heart disease due to arterio and atherosclerosis is at the present time thought to be based on aberrations of lipid metabolism and particularly cholesterol metabolism There is ample evidence that the liver is an important source of plasma cholesterol and cholesterol esters There is even more incriminating evidence to indicate that the liver is the source of the lipoprotein (S_f) molecules currently being accused of being the substance etiologically associated with this type of vascular disease (Pierce and Gofman) The phospholipids which also play a role in the cholesterol vascular deposits are also synthesized in the liver

Hypertension the co conspirator which with atherosclerosis is responsible for so many cardiac deaths and which has so far eluded exact etiologic detection may in part be dependent on functional aberrations of the liver It has been described in Chapter 65 page 485 that arterial blood pressure may depend on the equilibrium between the vasoexcitor (VEM) and vasodepressor (VDM) factors in the circulation VDM is chiefly elaborated by and entirely destroyed by the liver The evidence pointing to a disturbed equilibrium of these two substances in both human and experimental hypertension has been stated in Chapter 65 Liver dysfunction may conceivably play a role in the pathogenesis of human hypertension These relationships are summarized in Figure 86

THE EFFECT OF LIVER DISEASE ON THE HEART

It is quite obvious that disease of the liver an organ which is the pivotal point of many homeostatic mechanisms should have a profound effect on the heart at the helm of the body s circulation The chemical disturbances referred to above may have an etiologic relationship to various types of heart disease

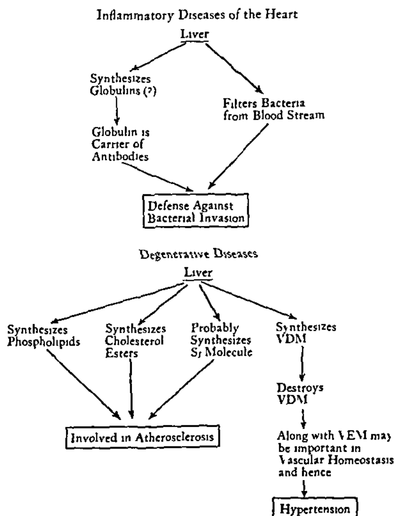


Fig. 86 Schematic presentation of the role of the liver in the pathogenesis of cardiovascular disease

Liver injury may have a profound and deleterious effect on the physiologic disturbances in congestive heart failure The liver influences the circulating blood volume by regulating the hepatic blood flow and vascularity Thus the liver can contribute to the hypervolemia of cardiac failure In addition the water and salt retaining tendencies in liver disease may accentuate the hypervolemia prevalent in heart failure Defective albumin synthesis resulting in hypoalbuminemia and decreased intravascular osmotic pressure would also tend to favor edema formation Indeed the suggestion has been made that the edema of heart disease may be partly attributable to hepatic dysfunction (Layne et al)

Increase of the extracellular fluid compartments has been demonstrated by the bromide method in patients with cardiac and hepatic decompensation (Ferraro et al) The similarity of the electrolyte and water disturbance in cardiac and liver disease has been alluded to (p 479) This consists of retention of sodium and water but loss of chlorides These defects are more marked in liver disease with ascites than in congestive heart failure Ascites even if it were due primarily to mechanical factors such as portal obstruction would reduce vital

capacity by pressure against and elevation of diaphragm Hepatic dysfunction with its resultant impairment of resistance to infection may invite various infections especially of the respiratory tract and then throw a further burden on the circulatory system

The synergistic effect of liver dysfunction on the pathologic physiology of cardiac failure is summarized in Fig 87

Disease of the liver may have a direct effect on the heart either because

1 the same etiologic agent attacks both organs

2 a similar metabolic aberration occurs in both

3 a metabolic defect damages both organs

4 severe hepatic damage results in systemic abnormalities which result in cardiac damage

The virus of yellow fever results in diffuse hepatic necrosis and also causes a myocarditis Syphilis is another example of the same infectious agent attacking both organs Viral hepatitis is rarely accompanied by myocarditis Lucke makes no mention of myocarditis in patients dying from hepatitis however occasionally this combination may occur (Fig 44b)

Chemical toxins may damage the myocardium at the same time that the liver is damaged Cardiac changes in malignant malnutrition of African natives has been pointed out (Chapter 41) The dietary deficiency probably causes independent lesions in both organs

Glycogen storage disease is an example of a metabolic disturbance which may attack both organs although the hepatic lesion is more common The metabolic defect of hemochromatosis at times results in cardiac as well as hepatic damage (Chapter 73) Finally severe hepatic necrosis causes hypothrombinemia and capillary damage which may in turn result in hemorrhages in various layers of the heart This is the probable pathogenesis of epicardial and endocardial hemorrhages seen in fatal hepatitis

Coexistence of Hepatic and Cardiac Disease

The emphasis on the interrelationship between cardiac and hepatic disease may lead to the erroneous conclusion that the two are always etiologically related This of course is not true A patient with any type of heart disease may become infected with the virus of hepatitis go on to development of post necrotic cirrhosis or develop a nutritional or biliary cirrhosis It is true that the disease acquired first may have exerted an influence on the subsequent disease The temptation is great to attribute the disease of both organs to the same etiologic agent or attribute the hepatic

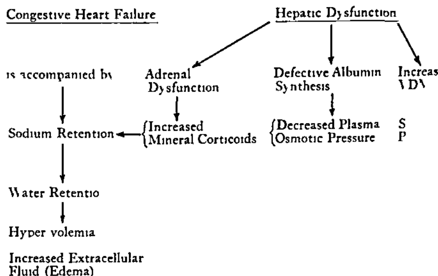


Fig 87 Schematic presentation of the synergism between the p thologic physi and congestive heart failure

disease to the cardiac abnormality The criteria for diagnosis of cardiac cirrhosis were discussed on page 49 The heart disease cannot be entertained as a cause of the liver disease if the latter definitely antedates the former Likewise intense jaundice decreased prothrombin level esophageal varices and evidence of widespread hepatic necrosis speaks for the noncardiac origin of the liver disease The decision as to the interdependence or independence of the cardiac and hepatic lesions in a given patient is no mere academic exercise but is of importance in directing the course of treatment and evaluating the prognosis

Diagnostic Confusion of Cardiac and Hepatic Decompensation

A patient with edema and ascites seen for the first time may offer diagnostic difficulties as to the etiology of these findings The confusion between edema of hepatic or cardiac origin may be especially difficult to resolve although purely renal factors may also have to be differentiated Anasarca of cardiac and hepatic origin have many biochemical similarities Retention of water and sodium occurs in both while chlorides are excreted readily This dissociation between sodium and chloride excretion may be even more marked in hepatic than in cardiac edema The extracellular fluid compartments are increased in both

There are many clinical similarities between cardiac and hepatic edema Cardiac as well as hepatic edema subsides at bed rest and may be accompanied by nocturia Dyspnea is of course more prominent in cardiac disease but may occur in hepatic disease when massive ascites interferes with the mobility of the diaphragms Orthopnea may also be present in ascites of hepatic origin Compression of the bases of both lungs by diaphragmatic elevation due to ascites results in basal crepitant rales simulating pulmonary passive congestion

The confusion is heightened by the fact that in hepatic edema circulatory factors play an accessory role by virtue of impaired renal blood flow while in cardiac edema hepatic dysfunction may play a role by disturbing the hormonal and humoral equilibrium (VDM adrenal corticoids pituitary antidiuretic substances (Fig 87)) The hypoproteinemia of cardiac disease which contributes to edema formation may result from hepatic dysfunction

Although edema of renal origin is not so commonly a source of diagnostic confusion it nevertheless has to be considered and ruled out First renal edema is not as common as the cardiac and hepatic types Second renal edema is universally accompanied by marked albuminuria as well as abnormal urinary sediment such as casts red cells etc The occurrence of albuminuria in congestive heart failure and occasionally in hepatic disease serves to complicate this differentiation However the intensity of albuminuria in renal disease with edema is marked while in the other conditions the edema is only mild or moderate The albuminuria of renal disease is accompanied by marked hypoalbuminuria and normal globulins while the hypoalbuminuria in hepatic or cardiac disease if marked is accompanied by hyperglobulinemia Serum cholinesterase determination may also help to differentiate the renal from the hepatic hypoalbuminemia (p 38) It should be added that renal disturbances are factors in primarily hepatic or cardiac edema

The clinician is therefore faced with the problem of deciding which organ-dysfunction is primarily responsible for the anasarca since some disturbance of 1) the liver 2) kidneys and 3) circulation may be present in edema originating initially from any of them To put it in a different way Does patient A with edema and ascites have

1 congestive heart failure?
2 decompensated liver disease?
3 renal disease?
4 heart disease and liver disease? If so
   a is the liver disease secondary to congestive failure that is cardiac cirrhosis?
   b is the liver disease independent of the heart failure?

A diagnosis of congestive heart failure is favored by

1 a history of old cardiac disease or pulmonary disease
2 onset of dyspnea and orthopnea prior to the development of edema and/or ascites
3 the presence of cyanosis

4 marked distention of neck veins
5 marked subcutaneous edema with absence of or moderate ascites
6 cardiac arrythmias
7 tachycardia that responds to digitalis
8 pulmonary congestion and pleural effusion in the absence of or with minimal ascites
9 megalocardia
10 increased venous pressure
11 increased circulation time
12 hypertension
13 diagnostic electrocardiographic changes

A diagnosis of hepatic failure is favored by

1 a history of alcoholism, malnutrition or previous hepatic disease
2 history of hematemesis (suggesting esophageal varices)
3 abdominal enlargement (ascites) prior to onset of dyspnea
4 onset of ascites prior to edema
5 marked ascites with minimal or moderate edema
6 marked jaundice
7 coma stupor lethargy, and any serious cerebral symptoms
8 fetor hepaticus
9 spider naevi
10 pectoral alopecia
11 splenomegaly
12 dilated periumbilical veins
13 marked disturbance of liver function tests especially those indicative of severe hepatic necrosis increased prothrombin time decreased antithrombin titre
14 marked hyperglobulinemia
15 esophageal varices
16 liver biopsy showing histologic changes in the liver

Renal edema is favored by

1 history of previous renal disease
2 recent respiratory infection
3 history of hematuria
4 marked albuminuria quantitative 5 to 10 grams every 24 hours or more
5 marked hypoalbuminemia with normal serum globulin
6 rising blood pressure or hypertension
7 urinary findings consisting of hematu pyuria cylindruria
8 progressive renal failure

The chief difficulty arises in differentia between cardiac and hepatic anasarca beca many of the differential features may be p ent in both but their degree and sequence *the differentiation* This has been noted in differential point listed above by the qualify adjectives Thus while ascites may be pre *in both* conditions it is more marked troublesome in hepatic disease Moreover relative intensity of edema and ascites dif in cardiac and hepatic disease The subcut ous edema *is the prominent feature in car* disease while ascites is the conspicuous feat of hepatic disease

While liver function tests are abnormal congestive heart failure as well as in prim hepatic disease the degree of abnormality the type of tests that are abnormal are helt in differentiation since as it has been poin out, grave degrees of hepatic failure do occur in liver disease of cardiac origin

When evidence pointing to cardiac and h *disease is found the differentiation* betw hepatic disease secondary to heart disease a hepatic disease of independent etiology m offer nearly insurmountable obstacles

The following patient presented the probl of determining the role of cardiac and hepa factors in the evolution of the clinical pictu

Case 11 This male 54 year old pati was admitted to the hospital in a semistupor state The history obtained at the time admission plus that which became availa later on consisted of the following five we before admission the patient developed dy nea swelling of the abdomen and edema the legs These symptoms became progressive worse The patient consumed inordin amounts of alcohol for 10 years Dietary inta was poor during the periods of increas alcoholic consumption

Physical examination was hampered by t severity of the patient s illness and his sem stuporou state Blood pressure was 110/ and pulse rate 9- There was marked dyspne some orthopnea and severe cyanosis Scler



F g 88 Need e b opsy of l er (X 100) of pa nt desc b d on p ge 50 Ma ked polym phonucle r and l}mphocy c nfil a on nc eased per po l and n alobular fib o s t ssue some d on f lobul a ch tectur \o denc of conges cirrho s comp t ble w h po al c hos s

were moderatel} cter c Subcutaneous edema was marked an l extended to the thorax The abdon nal wall w1s markedl\ w ter logged but in sp te of this ascites hepato negal} and splenomegal were eas l\ detected The l ver vas n arkedl} enlarged extend ng down to umb l cus \o sp der nae\ were present

Tl e heart tones ere d tant and n nur murs were aud ble Tl e card ac contour co ld not be leterm ned b\ percus on because of the e le n 1 of the che t w ill B lateral basal rale were au l ble Il e neck \e ns ere not marke ll l tended

Tl e pat ent s stupor cter1 s asc tes l epato splen negal and alcol ol c h story led to 1 d agn of portal cirrl o tl l ver fa l re and ana arca It wa 1ot clear hat role f an\ heart fa lure pla e l n tl s p cture The tach\ car l a nl\ n oderate and sp ke ag1 t heart t1 l re The l asal rales were expl1 nal le n tl e l a t the a c tes an l general ze l ede na Aga n t h art ta l re was the m xlerate rthopnea

I al orator\ test reveale l a prothroml n t e t 19 ec n ls (normal 13) th\ n ol turb d t\ t 3 un t cepl al n cholesterol flocc lat on 3+ total prote n 5 8 gm% of wh ch 2 8 vas alb m n and 3 0 globul n total serum l l rub n 4 0 n g prompt react ng 4 mg alkal ne pl os pl ata e 9 6 Bodan k\ un ts total cholesterol 04 n g esters 75% serum sod um 148 mFq per l ter \\l le the l \er funct on te t sl owe l unquest onable abnormal t\ the changes ere not a marke l as one woul l expect n sucl a gra\el ll pat ent if all the cl n cal find ng ere attr l utal le to l \er d ease

Abdo n nal paracente \ elde l al out 1500 cc of clear str1w colore l fl d w th a spec fic gra\it\ of 101

A roentgenogram of cl est re\ealed a mark edl\ enlarged heart with pre lom nant enlarge n ent of left \entricle Electr card ogra n re\eale l a first degree atr o \e itricular block intra\entr c lar l lock and other changes sug gesti\e of recent m\ocar l al infarct on These fin l ngs in l cated tl at the heart and c rcula tor\ fa lure ere factors n the cl n cal p cture The que t on tl en aro e whetl er the hepat c cl anges were secondar\ t heart fa lure S nce th s was the first ep ode of fa lure t seemed unl kel\ that the l \er injur\ was secon lar\ to the car l ac deco np n at on

The patient responded to combined therapy directed to cardiac and hepatic failure This included digitoxin mercurial diuretics intravenous glucose in distilled water supplementary vitamins liver extract vitamin K and eventually a high protein high carbohydrate diet

Remarkable clinical improvement became evident Liver function tests likewise improved When the prothrombin time decreased to 14 seconds liver biopsy was done

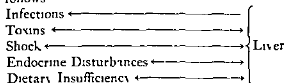
Liver biopsy (Fig 88) showed no evidence of central necrosis but distortion of lobular pattern by strands of fibrous tissue Many hepatic cells showed cloudy swelling nuclear changes and other evidence of degeneration Abundant leukocytic infiltration was present The morphological changes in the liver favored a process independent of the cardiac disease This was also favored by the fact that in spite of disappearance of anasarca and cardiac compensation with a return of the plasma protein to normal (albumin 3 9 gm% globulin 3 1 gm%) the bromsulfalein test showed 30% retention at 45 minutes

This case illustrates clearly the difficulties *encountered in differentiating between cardiac* and hepatic anasarca and if both heart and liver failure concur the difficulty in assigning the proper role to each in the clinical picture All available technique had to be utiliz d to clarify the issues Liver biopsy was of considerable help

67 — *The Liver in Shock and Anemia*

The Effect of Shock on the Liver

It seems that all pathologic processes and injurious agents that affect the liver are in turn affected by it And thus it is with shock[1] The role of the liver in induction of irreversible shock by liberation of VDM is discussed on page 485 The liver in turn is profoundly affected by shock which lasts for a considerable period of time This role of the liver in defending the organism against noxious processes and agents can be likened to a guard defending the entrance to a castle who while carrying out this *task is injured or destroyed The vulnerability* of the liver carrying out the hazardous functions can be expressed diagrammatically as follows



Pathogenesis of Liver Injury in Shock

The liver is very vulnerable to anoxia The drop in arterial pressure not only results in hepatic damage but the hepatic anoxia plays a role in the irreversibility of the shock This was demonstrated clearly by Frank and co workers who prevented irreversible shock by vivi perfusion of the liver When the hepatic circulation was maintained by infusion of blood into the splenic vein the shock remained reversible Equal hypoxia of other tissues did not result in irreversible shock and infusion of *blood into the jugular vein* did not prevent irreversible shock As it was pointed out hepatic hypoxia may result in increased elaboration of VDM which in turn causes irreversible shock (Chapter 65) Shock also results in disorganization of some of the important enzyme systems in the liver (Wilhelmi and Long) It is worth referring to one paradoxical fact that is the survival of dogs and some human beings of

ligation of hepatic artery which it seems must produce a profound hypoxia even if some of the collateral are not interrupted

The duration of the shock is an important factor in the production of the hepatic lesion One gathers from the data presented by Ellenberg and Osserman that shock of less than 10 hours duration produces no hepatic changes or only very mild ones while shock of over 24 hour duration produces characteristic changes The severity of the shock also plays a role in the production of the hepatic lesion That anoxia is the important etiological factor rather than blood loss is demonstrated by identical pathological changes in individuals dying from exposure to low atmospheric pressures (Moon)

The nature of the specific pathologic changes in the liver resulting from shock has received some enthusiastic discussion in the recent literature especially in regard to its similarity or dissimilarity to the lesions seen in congestive failure The hepatic lesions in shock like in congestive failure are chiefly centrolobular but the hepatocellular damage may be diffuse and inconstant (Moon) The opinion has been expressed by several workers that centrolobular necrosis can be produced only by anoxia of shock and not by congestive failure And when congestive failure is accompanied by centrolobular necrosis shock must have been a part of the picture (Clarke 1948 Ellenberg and Osserman 1951) The contradictory statements in medical literature may be stimulating to the investigator but must indeed be bewildering to the student and practitioner of medicine who tries to understand clinical problems in an orderly fashion The workers who insist that there is a marked distinction between lesions due to shock and those due to congestive heart failure claim that shock produces central necrosis while the other produces only degeneration and atrophy The analysis of their post mortem material seem to support this contention However speaking of the changes in shock Clarke states When the dead liver cell were absorbed there remained sinusoids filled with blood and the lesions than became indistinguishable from those of passive congestion This implies that liver cells do disappear in passive congestion therefore they must have died and hence be necrotic Since anoxia is the critical injurious factor in shock why cannot the anoxia of heart failure result in similar hepatic damage?

Centrolobular necrosis has been produced experimentally by partial constriction of the inferior vena cava in dogs above the hepatic veins (Zimmerman and Hillsman) Moschcowitz speaking of the effect on the liver of cardiac failure refers to the occurrence of extensive centrolobular necrosis and this in patients with mitral stenosis not associated with shock On the other hand degenerative changes which some attribute chiefly to passive congestion are noted in shock Moon noted degeneration and fatty changes in addition to necrosis in patients dying from shock

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The hepatocellular injury resulting from shock is reversible if the shock is reversible Regeneration of the destroyed cells occurs very quickly and in an orderly fashion since the reticulum framework remains intact

The Effect of Shock on the Liver—Summary

Shock results in
- **Hypoxia to which**
  - **Liver is very vulnerable**
    - **Destruction of enzyme systems (Cocarboxylase and cozymase)**
    - **Increase in circulating VDM irreversible shock**

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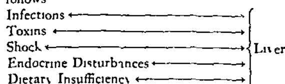
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    - **Destruction of enzyme systems (Cocarboxylase and cozymase)**
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The pat ent re pon led to con b ned therapy d rected to card ac and l ep t c fa lure Tl s ncluded d g tox n merc al d u et cs intra venous glucose in d st lle l ater supple mentary vitam ns l er ext act tan n K and e entually a l gl p ote n h gh carbo hydrate d et

Remarkable cl cal n p ement beca e ev dent Liver f nct on te ts l ke v e npro ed When the prothromb n time decrea ed to 14 seconds l ver b opsy vas done

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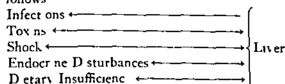
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67—The Liver in Shock and Anemia

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The duration of the shock is an important factor in the production of the hepatic lesion One gathers from the data presented by Ellenberg and Osserman that shock of less than 10 hours duration produces no hepatic changes or only very mild ones while shock of over 24 hours duration produces characteristic changes The severity of the shock also plays a role in the production of the hepatic lesion That anoxia is the important etiological factor rather than blood loss is demonstrated by identical pathological changes in individuals dying from exposure to low atmospheric pressures (Moon)

The nature of the specific pathologic changes in the liver resulting from shock has received some enthusiastic discussion in the recent literature especially in regard to its similarity or dissimilarity to the lesions seen in congestive failure The hepatic lesions in shock like in congestive failure are chiefly centrolobular but the hepatocellular damage may be diffuse and inconstant (Moon) The opinion has been expressed by several workers that centrolobular necrosis can be produced only by anoxia of shock and not by congestive failure And when congestive failure is accompanied by centrolobular necrosis shock must have been a part of the picture (Clarke 1948 Ellenberg and Osserman 1951) The contradictory statements in medical literature may be stimulating to the investigator but must indeed be bewildering to the student and practitioner of medicine who tries to understand clinical problems in an orderly fashion The workers who insist that there is a marked distinction between lesion due to shock and those due to congestive heart failure claim that shock produces central necrosis while the other produces only degeneration and atrophy The analysis of their post mortem material seems to support this contention However speaking of the changes in shock Clarke states When the dead liver cells were absorbed there remained sinusoids filled with blood and the lesions than became indistinguishable from those of passive congestion This implies that liver cells do disappear in passive congestion therefore they must have died and hence be necrotic Since anoxia is the critical injurious factor in shock why cannot the anoxia of heart failure result in similar hepatic damage?

Centrolobular necrosis has been produced experimentally by partial constriction of the inferior vena cava in dogs above the hepatic veins (Zimmerman and Hillsman) Moschcowitz speaking of the effect on the liver of cardiac failure refers to the occurrence of extensive centrolobular necrosis and this in patients with mitral stenosis not associated with shock On the other hand degenerative changes which some attribute chiefly to passive congestion are noted in shock Moon noted degeneration and fatty changes in addition to necrosis in patients dying from shock

There is no doubt that patients who develop shock superimposed on congestive heart failure such as occurs in myocardial infarction are more likely to develop centrolobular necrosis than individuals who suffer from heart failure The fact that some patients die after many recurrent episodes of heart failure without showing centrolobular necrosis cannot be accepted as proof that congestive heart failure never results in central necrosis The degree of anoxia as well as the degree of the intrahepatic venous hypertension may vary in different types of heart failure and this variation may account for the variable response The rapidity of onset of anoxia may be an important consideration since a cell can adjust more easily to a gradual than a sudden reduction in oxygen

The hepatocellular injury resulting from shock is reversible if the shock is reversible Regeneration of the destroyed cells occurs very quickly and in an orderly fashion since the reticulum framework remains intact

The Effect of Shock on the Liver—Summary

Shock results in
- **Hypoxia to which**
  - **Liver is very vulnerable**
    - **Destruction of enzyme systems (Cocarboxylase and cozymase)**
    - **Increase in circulating VDM irreversible shock**

Morphological alteration
Central necrosis depends on
Duration and
Severity of shock (hypoxia)

Anemia and Liver Disease

Effect of Anemia on the Liver

A sudden loss of blood from hemorrhage that is an acute anemia results in centrolobular necrosis. Severe anoxia has been implicated here as well as in patients developing liver injury from exposure to low atmospheric oxygen. However, the hepatic damage in the case of hemorrhage is due to the concomitant drop in blood pressure (shock). If the blood pressure and circulation are maintained, hepatic necrosis does not occur in spite of the decreased amount of oxygen per unit of blood. In the presence of chronic anemia the liver is more vulnerable to noxious agents, but acute necrosis depends upon decreased oxygen tension rather than the decreased amount of oxygen carried in the blood. It is possible that the increased cardiac output and accelerated circulation compensates in part for the decreased oxygen carrying capacity of the blood. The anemic liver is therefore more vulnerable to circulatory impairment.

The relative innocuousness of profound chronic anemia has been demonstrated in a study of patients with untreated pernicious anemia (Schilling and Harris 195[illegible]). Hepatic dysfunction was mild, not universal and showed no definite pattern. Bromsulfalein retention of moderate degree was noted in a few patients. The flocculation tests were normal.

Effect of Liver Disease on the Blood

While anemia does not have any startling effect on the liver, the liver does have a profound effect on the blood count. The problem of the type of anemia in liver disease and its pathogenesis has received a good deal of attention in the literature. It is not surprising that liver disease is frequently associated with anemia, since the liver plays an important role in hemoglobin synthesis and red cell maturation. In the normal adult the liver does not function as a hematopoietic organ but it is important in the following: 1. hemoglobin synthesis, 2. iron storage and 3. storage of the antianemic factor.

Whipple and associates (1945) have demonstrated that the Eck fistula dog does not synthesize hemoglobin at a normal rate, and iron given intravenously as well as orally is not utilized in a normal fashion in the synthesis of hemoglobin. The liver is an important site of iron storage (Chapter 73). Various attempts have been made to correlate serum iron with hepatic damage. There is a lack of general agreement as to what happens to the serum iron value in various forms of liver disease, but most observations point to some abnormality. The normal serum iron values vary between 40 and 150 gammas per 100 cc. Massarin and Delp have noted elevated serum iron values in hepatocellular damage (hepatitis); in some cases these values were over 400 grams. These workers attribute these elevated iron values to liberation of the element from the destroyed liver cells. The elevated serum iron may also be due to hemolysis. The iron values return to normal with recovery. Abnormal serum iron values in cirrhosis and hemochromatosis are mentioned (Chapters 15 and 73). The storage of the antianemic factor needs no elaboration at this time.

The Anemia of Liver Disease

In analyzing the anemia of liver disease one must also keep in mind the tendency to hemorrhage in hepatic disorders from esophageal varices or due to hypoprothrombinemia or capillary injury. Complicating infections may also be responsible for anemia. The anemia of liver disease may be of macrocytic, normocytic or microcytic type. The macrocytic and normocytic hypochromic anemias are most commonly encountered. When a microcytic anemia is present, hemorrhage should be suspected. Wintrobe, in a study of 132 patients with various types of liver disease, found macrocytic anemia in 32.6%, normocytic anemia in 30.3%, and microcytic anemia in 14.4%, and no anemia in 22.7%.

The macrocytic anemia is particularly intriguing because of its possible relationship to pernicious anemia and the storage of the antianemic factor. Wintrobe found macrocytic anemia chiefly in patients with severe cirrhosis

and in cirrhosis associated with malignancy. He did not find this type of anemia in acute liver disease or those with slight or moderate hepatic involvement. Berman and coworkers (1949) found anemia in 84% and macrocytosis in 75% of their patients but no correlation between the severity of liver disease and anemia or macrocytosis was made. Meulengracht and Gormsen in their study of 24 women with subacute and chronic infectious hepatitis found the average size of the erythrocytes increased in over 50% of their patients but no pernicious anemia-like picture was found in any. The anemia was moderate in degree and hypochromic and normochromic as well as hyperchromic.

In considering the pathogenesis of the macrocytic anemia in liver disease it seems logical to espouse defective storage of the hematopoietic principle as the responsible factor (Wintrobe). An occasional patient with macrocytic anemia and liver disease has been found who responds to liver extract therapy. This may be due either to coexistence of pernicious anemia and liver disease or to improvement of the liver disease from liver extract or to other concomitant therapy. That pernicious anemia is not present in the majority of cases of macrocytic anemia of liver disease is evident from the hematological picture, the erratic response to specific therapy, and the presence of free hydrochloric acid in most patients with this type of anemia. The "intrinsic factor" was demonstrated in the gastric juice of the patients with this type of anemia (Wintrobe and Shumaker). The theory that the macrocytic anemia is due to defective storage was supported by finding an absence of this principle in the liver of one patient dying from cirrhosis, while it was present in the liver of another patient who died from acute hepatic necrosis (Goldhamer et al.). This in itself seems paradoxical, since in widespread acute necrosis the massive destruction of liver cells should render this organ less capable of storing the antianemic factor. Schiff and coworkers refuted the hypothesis of defective storage of the antianemic factor in patients with liver disease by obtaining favorable reticulocyte response in pernicious anemia patients receiving extract of these livers. Three of these patients with hepatic macrocytic anemia showed no response to liver extracts during life.

Several other explanations have been invoked for the macrocytosis of liver disease. Reticulocytosis is frequent in liver disease and since the reticulocyte is larger than the mature erythrocyte its increase in the peripheral blood would increase the average diameter of the erythrocyte (Rosenberg and Walters). Alcohol addicts were also found to develop anemia and macrocytosis, but these blood changes did not parallel hepatic enlargement or dysfunction. It was therefore postulated that the macrocytosis is not due to liver damage but rather to bone marrow damage by the deficiency of some dietary principle (Bianco and Jolliffe, 1938). Meulengracht and Gormsen (1949) attributed the macrocytosis in their patients to osmotic changes in the erythrocytes produced by a hypothetical substance circulating in the serum. Patients with macrocytosis and liver disease have an increased blood volume. This increased blood volume without corresponding increase in the number of erythrocytes gives a reduced number of erythrocytes per cubic mm., although the circulating cell volume may be normal or only slightly subnormal (Bateman et al., 1949).

Alterations in the bone marrow have been noted and these may be the basis of the changes in the peripheral blood. These alterations are not compatible with pernicious anemia. Megaloblastic erythropoiesis has not been observed in liver disease. The bone marrow shows normal or increased cellularity and there is extension of hematopoiesis to the shafts of long bones. The marrow presents a picture of macronormoblastic erythropoiesis (Berman et al.). Some increase in plasma cells of marrow has been noted and may be related to hyperglobulinemia (Meulengracht).

Hemolytic anemia has also been noted in association with liver disease. The increased reticulocyte count and occasionally an increased amount of bile pigment output with a low grade anemia are suggestive of hemolysis (Watson, p. 83). The possibility of a toxic substance or hemolysin originating from the damaged liver exists, but this hypothesis is unproven. Changes in the red cell occur in liver disease as evidenced by the "target" cells

in infectious hepatitis Hemolytic anemia arising secondarily to liver disease is of the acquired or symptomatic type The Coombs test has been found positive in some of these cases

When hemolytic anemia is found in association with liver disease the most likely assumption is that the liver disease is secondary to the hemolytic process The reaction of the liver to hemolytic anemia is discussed more fully on page 81 Suffice it to state here the liver may be damaged by the anoxia coupled with increased demand for pigment excretion and increased viscosity of the bile or as result of hemosiderin deposition from repeated transfusions (exogenous hemochromatosis Chapter 13 Fig 13)

In the presence of a severe anemia with marked splenomegaly the likelihood of hemolytic anemia preceding and independent of liver disease must be considered Hyman and Southworth have recently reported the association of hemolytic anemia in 3 patients with severe liver disease and referred to 18 other cases found in the records of the Presbyterian Hospital of New York In two of the patients described *in detail an anemia of considerable* severity seemed to precede the development of liver disease One of these showed hemosiderosis of liver and spleen The third patient a 17 year old girl *with mild macrocytic anemia* had intense jaundice splenomegaly and dilated abdominal veins A 5100 gm spleen was removed during the construction of a splenorenal shunt The liver was shrunken nodular and revealed portal cirrhosis and periportal necrosis

Several other cases outlined by Hyman and Southworth indicated the preexistence of liver disease In the eight cases in which liver biopsy was available the liver damage was thought to be secondary to hepatitis In addition to a positive Coomb s test some of these patients showed increased erythrocyte fragility The spleen was markedly enlarged in all these patients and this organ may play an important role in the production of the hemolytic syndrome

Leucopenia and thrombocytop
nomegaly if assoc ... p
sion of chronic l ... ch
ble for the le
e ... l

bocytes may reach very low levels The leucocyte count is frequently below 6000 and in some cases may decrease to 1000 cells per cu mm of blood The leucopenia may impair the individual s resistance to infection while the thrombocytopenia increases the bleeding tendency along with hypoprothrombinemia erosion of esophageal varices and increased capillary fragility

Treatment of Anemia and other Hematological Abnormalities Secondary to Liver Disease

Iron salts such as ferrous sulfate administered orally are usually ineffective Occasionally this is effective in the hypochromic microcytic anemia associated with liver disease When this is the case the probability exists that the anemia is due to blood loss In other types of anemia iron administration is useless wasteful and may be harmful Parenteral iron administration is especially harmful because of the difficulty in its excretion it may be deposited as hemosiderin and further impair the liver (Chapter 73)

Blood transfusion is indicated when the anemia is significant It is the most effective therapeutic agent It should be given with caution in the presence of esophageal varices Liver extract is usually not effective even in the macrocytic type of anemia but because of its possible value in the treatment of liver disease can be used with this objective in mind Intensive treatment of the primary liver disease should be in the foreground of the treatment of any of its complications

Splenectomy produces an excellent response in the leucopenia and thrombocytopenia associated with splenomegaly I have seen prompt rise of both these elements after splenectomy When esophageal varices are associated with the splenomegaly splenorenal venous anastomosis should be done at the same time

Treatment of Hematological Abnormalities—Summary

A Anemia
  1 Iron Salts orally
    of some value in hypochromic *microcytic anemia due to* hemorrhage

of no value in other types of anemia
parenteral administration hazardous because of production of hemosiderosis
2 Blood Transfusion
indicated and most effective in severe anemia
caution should be used in esophageal varices may increase bleeding
3 Liver Extract
is ineffective even in macrocytic anemia
may be of some help in treatment of liver disease
4 Treatment of primary liver disease most important
B Leucopenia and Thrombocytopenia
1 Splenectomy when splenomegaly is present
2 Transfusions are helpful

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The Liver in Gastrointestinal Disorders

Peptic Ulcer and Liver Disease

Peptic ulcer because of its great frequency obscure etiology and often present diag ostic and therapeutic difficulties is a constant ource of irritation to the busy physician Its elationship to other diseases may throw some ight on its etiology and aid in detection and reatment The relationship of peptic ulcer to he liver is fourfold

1 The frequency of peptic ulcer in liver disease Does liver disease contribute to the athogenesis of peptic ulcer?

2 The frequency of liver disease in peptic ulcer Does peptic ulcer contribute to the levelopment of liver disease?

3 Is their coexistence dependent upon a imilar etiologic agent or are they merely oincidental?

4 What diagnostic and therapeutic problems ari e from their coexistence?

Does Liver Disease Result in Increased Susceptibility to Peptic Ulcer

The role of liver disease in the development of peptic ulcer is obscure and paradoxical Patients with severe liver disease have a tendency to lower gastric acidity and this should be expected to give them some degree of protection against peptic ulceration On the other hand exclusion of bile secretions from the intestinal tract has been repeatedly demonstrated to result in gastrointestinal ulceration In severe liver disease bile excretion may be markedly reduced or altered chemically The experimental work dealing with the effect of biliary obstruction and biliary fistula on the production of gastrointestinal ulcers has been thoroughly reviewed by Ivy and his associates in the monograph Peptic Ulcer While some observations seem to indicate that the loss of the neutralizing or buffering action of bile may be responsible for the greater susceptibility to ulceration this is not conclusive My casual clinical observations contradict this theory I have seen bile stained gastric contents in many patients with gastric and duodenal ulcers which were intractable and unresponsive to therapy in spite of their contact with bile In the Mann Williamson operation bile is diverted from the jejunum but pancreatic juice which is more alkaline is also excluded

Eck fistula may result in peptic ulceration

in a small percentage of animals While this may be due to disturbed hepatic function it is more likely caused by the disturbed circulation Indeed the portal hypertension of cirrhosis with the resultant venous engorgement of the stomach from the collateral circulation may contribute to reduced mucosal resistance and ulceration It has been demonstrated by Baronofsky and Wangensteen that splenic or portal vein obstruction results in increased susceptibility of dogs and rabbits to experimental gastric and esophageal ulceration

The nutritional deficiency and hypoproteinemia associated with severe liver disease may be a contributory factor to peptic ulceration Weech and Page in their study of nutritional edema in dogs noted the development of peptic ulcer in over one third of the animals Peptic ulcer in patients with liver disease may develop through such mechanism Ingestion of large amounts of alcohol which is common in cirrhosis is also known to produce hyperemia edema and superficial erosions of the gastric mucosa The alcoholism of cirrhosis therefore may be an etiologic factor in the production of peptic ulcer Another toxin which is known to produce peptic ulceration as well as liver damage is cinchophen While the toxin plays no role in the usual clinical cases of cirrhosis nor in the superimposed peptic ulcer the possibility may be raised that some unknown toxin wh ch causes liver injury may also cause injury to the gastrointestinal mucosa

It has been my impression for some time that peptic ulcer is more common and runs a more precarious course in patients with cirrhosis Although the two diseases occur most commonly in a similar age group and sex their coexistence seems to me more than coincidence Bjorneboe and Raaschou found gastric ulcer in 10 2% of patients with subchronic atrophy of the liver but in only 2 6% of those with Laennec s cirrhosis Lipp and Lipsitz found peptic ulceration in 11 5% of patients with portal cirrhosis and in 14 3% of patients with biliary cirrhosis but in only 6 6% of the control group of similar age One is tempted to speculate that the slightly greater incidence of peptic ulcer in patients with biliary cirrhosis than in those with portal cirrhosis is due to the exclusion of bile from the gastrointestinal tract

Although the evidence is not conclusive it at least favors the assumption that severe liver disease does predispose to the development of gastroduodenal ulceration through one or several of the following mechanisms

1 Exclusion of bile from the intestines
2 Reduction of bile entering the intestines
3 Abnormality of the bile secreted
4 Irritating effect of circulating bile products
5 Local circulatory disturbances portal hypertension
6 Hypoproteinemia
7 Malnutrition
8 Alcoholism
9 Other toxins which may injure the liver and the gastrointestinal mucosa simultaneously

Does Peptic Ulcer Tend to Produce Liver Disease

I am not impressed with this as with the reverse of this question And yet Schnitker and Haas found a greater incidence of morphologic abnormalities in the liver of ulcer patients than in the control group Goldbloom and associates found no increased incidence of hepatic dysfunction in patients with uncomplicated peptic ulcer However in autopsy material these observers found histologically normal livers in only 8% of 62 patients dying with peptic ulcer as one of the diagnoses Fatty changes were found in 53% and cirrhosis in 5 or 15% of the group This is a very high incidence of hepatic diseases but Goldbloom and his coworkers attributed them to the associated lesions found rather than to the peptic ulcer Mateer and his associates studied 31 operated cases of peptic ulcer by means of surgical liver biopsy and liver function tests They found a histologically normal liver in only 7% and 48% of this group showed one or more abnormal tests Since this group of cases did not have severe associated diseases these disturbances could be attributed to the peptic ulcer or its treatment

At least up to recently the restricted diets prescribed for ulcer patients could result in various dietary deficiencies If the physician is not on guard vitamin deficiencies and protein deficiency can result Complicating hemorrhage or slow blood loss may contribute to

protein depletion Administration of blood transfusions increases the hazard of developing a viral hepatitis Surgical treatment of peptic ulcer introduces trauma and the deleterious effect of surgery on the liver (Fig 63) I have seen hepatitis developing several months post operatively probably as a result of blood transfusions

Post Hepatic Jaundice in Peptic Ulcer

The occurrence of jaundice of an obstructive nature from peptic ulcer is rare but it has been described It is alluded to on page 91 Jaundice as a direct result of peptic ulcer is extremely rare and when it occurs it is due to a duodenal rather than gastric ulcer One would expect it to develop more commonly from post bulbar ulcer because of the proximity of this ulcer to the papilla of Vater Engel and Spann reported a female patient who developed jaundice from a localized perforation of a duodenal ulcer with inflammatory obstruction of the common duct Levine and Gordon reported a case of duodenal ulcer with jaundice which apparently subsided after perforation of the ulcer Engel and Spann suggest that the latter case was probably similar to theirs and that a localized perforation caused the jaundice but rupture of this localized inflammatory pocket resulted in the generalized peritonitis and the relief of the common duct obstruction Parks and Fitz in 1939 found 35 cases of obstructive jaundice from duodenal ulcer and added one of their own Another case was recently (195) reported by Stephenson and coworkers

The Problem of Coexistence of Peptic Ulcer and Liver Disease

The coexistence of peptic ulcer and cirrhosis regardless of their causal relationship presents difficult and occasionally insurmountable problems in diagnosis and therapy Clarification of this problem is especially difficult when the liver disease is of marked severity and there is complicating hemorrhage Patients under therapy for cirrhosis should have frequent gastrointestinal roentgenograms to determine the presence of esophageal varices During these examinations the duodenum and stomach should be watched for peptic ulcers On the other hand patients with peptic ulcer should have an occasional evaluation of liver function Such careful study of the patient is helpful when a massive gastrointestinal hemorrhage occurs

It is but natural to assume that a patient with advanced liver disease who develops an upper gastrointestinal hemorrhage is bleeding from esophageal varices Such an assumption is not always correct I have seen several patients with advanced cirrhosis who developed a hemorrhage from a coexisting peptic ulcer One patient was particularly remarkable A fifty four year old man with a known alcoholic history who had been treated for several years for portal cirrhosis of the liver entered the hospital in a semi comatous state A history of recent profuse hematemesis was obtained He was moderately jaundiced A faint fetor hepaticus was noted Jaundice spider nevi massive ascite visible abdominal veins and hepato splenomegaly completed the picture of advanced cirrhosis and hepatic failure This was an obvious case of bleeding esophageal varices! This diagnosis was discredited by finding at autopsy a large prepyloric ulcer with an eroded artery as the source of hemorrhage Esophageal varices were also found but they were intact and not bleeding

In such a case with advanced hepatic failure a correct diagnosis would not alter the therapy or improve the prognosis No surgeon would attempt gastric surgery in a patient in hepatic coma This case does emphasize that even in advanced cirrhosis with esophageal varices the hemorrhage may arise from a coexistent ulcer this differential diagnosis may be life saving if the liver disease is not so far advanced as to preclude surgery

The reverse of the above problem also arises and is equally difficult to solve Namely when a patient with a known peptic ulcer develops a gastrointestinal hemorrhage there is no assurance that the bleeding is from the ulcer One must keep in mind the second commonest cause of upper gastrointestinal bleeding—esophageal varices A deformed duodenal bulb is no guarantee that it is the site of bleeding Demonstration of a crater is a more reassuring sign Simultaneous compression of the distal esophagus by balloon and aspiration of the stomach are helpful procedures in the differ

ential diagnosis For if no blood is aspirated from the stomach the assumption is justified that the bleeding is not distal to the esophagus For complete differential diagnosis of hemorrhage from peptic ulcer and esophageal varices see page 352 It should be reemphasized that if both diseases coexist all diagnostic features may favor one disease whereas the other disease is responsible for the hemorrhage as is illustrated by the case cited

Treatment

In the therapy of either peptic ulcer or cirrhosis (uncomplicated) one should strive to prevent the other condition Thus in the therapy of peptic ulcer one should insist on a well balanced diet high in proteins and supplemented with vitamins It goes without saying that alcohol and other toxins should be avoided In the treatment of liver disease frequent feedings are indicated and these may minimize the likelihood of peptic ulceration The awareness of the association of these two diseases should keep the clinician on the lookout for this combination When their coexistence has been established the treatment may have to be modified The frequent milk cream feedings may have to be changed to milk alone to avoid an excessive amount of fat On the other hand the high protein diet containing a good deal of meat may not be well tolerated by a patient with an active peptic ulcer Eggs and cheese should be used more liberally The neutralization of gastric acidity by alkalies can be utilized to the full since it may be useful in preventing erosions of esophageal varices Sodium bicarbonate which is not the alkali of choice for the treatment of peptic ulcer should not be used at all in the presence of liver disease because of the tendency to sodium retention

If upper gastrointestinal hemorrhage occurs the alternate sources of hemorrhage must be kept in mind Esophageal tamponade may be instituted for diagnostic as well as therapeutic reasons For elaboration of the therapy of bleeding esophageal varices see page 355 If bleeding does not cease it is imperative to decide whether the bleeding is from esophageal varices or peptic ulcer since emergency surgery may be indicated in the latter but not in the former If intractable hemorrhage originates from a peptic ulcer in a patient with cirrhosis of the liver surgery may be undertaken unless the liver disease is so advanced as to preclude recovery The risk of course is much greater than in an otherwise normal individual because of the poor response of patients with liver disease to surgical procedures However, if bleeding continues in spite of medical treatment there is little alternative Blood transfusions should be used liberally both pre and post operatively to avoid prolonged shock with the resultant centrolobular necrosis (p 504)

The type of surgical procedure must be evaluated in each case but the aim should be to stop the bleeding in the quickest and simplest manner Gastric resection should be undertaken only 1 when this is the only procedure that can be relied on to stop bleeding 2 when the hepatic disease is latent and does not markedly increase the risk from extensive surgery 3 when the ulcer is gastric and may be malignant Vagotomy combined with ligation of the bleeding vessel may be the operation of choice in this complicated situation because this would entail a smaller surgical risk

The Liver in Ulcerative Colitis

Ulcerative colitis being a chronic debilitating disease accompanied by infection may be expected to result in hepatic injury Pylephlebitis and pyogenic liver abscess secondary to ulcerative colitis are discussed in Chapter 26 Here the discussion will be confined to non suppurative hepatic disease The following factors contribute to the development of hepatic injury in ulcerative colitis

1 chronic malnutrition
2 chronic infection
3 protein depletion from the chronic diarrhea and
4 frequent blood transfusions as a source of the S H virus

Type of Liver Disease

The types of liver disease which are known to complicate ulcerative colitis include

1 Degenerative changes
   a Fatty degeneration
   b Amyloidosis

Inflammatory changes
a Foci of inflammation
b Interlobular hepatitis
c Viral hepatitis
3 Cirrhosis

While the nature of this baffling disease of the colon and its treatment subjects the patients to the hazards of hepatic injury it can not be maintained with equal logic that hepatic diseases predispose to the development of ulcerative colitis However hepatic disease both acute and chronic produce changes in the gastrointestinal tract and preexisting hepatic dysfunction can have a deleterious influence on any serious disease Thus again we see this interplay of forces Ulcerative colitis leading to liver injury and liver disease influencing the clinical course of ulcerative colitis

Incidence of Various Types of Liver Injury in Ulcerative Colitis

The analysis of the incidence and classification of liver disease occurring in ulcerative colitis depends upon the approach to the problem morphological or functional Morphological observation of hepatic changes were reported as early as 1919 by Logan who found a high incidence of liver disease fatty infiltration in 10 of 13 patients and cirrhosis in one The frequency of fatty livers in patients dying from ulcerative colitis is confirmed by more recent observations although the incidence is not as high as cited above In the series from the Mayo Clinic fatty infiltration occurred in 5 % of 91 cases (Jones et al) Kimmelstiel and associates found fatty changes in 15 % of their cases (Table 69) The cases reported from the Lahey clinic showed significant fatty infiltration in 11 of 9 patients Slight fatty infiltration was considered insignificant by these authors (Ross and Swarz) They suggested that their control series showed a similar incidence of hepatic change Jones and his associates found a definitely higher incidence and severity of fatty infiltration in their patients with ulcerative colitis as compared with an unselected control group of autopsies and a control group with peritonitis This was also the experience of Kimmelstiel and associates (Table 69)

TABLE 69

The Incidence of Morphological Changes in the Liver in Patients with Ulcerative Colitis

	[illegible]	[illegible]	[illegible]
	Number	Per Cent	Per Cent
Degenerative lesions			
Cirrhosis	1	1 08	2 3
Pseudolobulation		15	0 8
Multiple Bile Casts		2 15	0 4
Necrosis and Dissociation	8	8 60	6 6
Fatty Changes	14	15 05	1 4
	7	9 03	11 5
Inflammatory lesions			
Interlobular Hepatitis	9	9 68	1 1
Foci of Inflammation		5 38	1 0
	14	15 06	2 1

From Kimmelstiel et al Am J Path 8 259 1952

Pollard and Block also found fatty degeneration very frequently in their group of cases

Cirrhosis while not as common as fatty infiltration of the liver is also significantly increased Three patients of the 9 from the Mayo Clinic showed cirrhosis and one of the 9 patients reported by Ross and Swarz showed well developed cirrhosis Tumen and his associates found 5 instances of cirrhosis among 151 patients with ulcerative colitis The diagnosis in 4 of these patients was established by peritoneoscopy

Needle biopsy of liver may throw further light on this problem A study of this type was carried out by Kleckner and associates who found 6 instances of cirrhosis in patients with ulcerative colitis The increased incidence of cirrhosis in ulcerative colitis is not borne out in all studies (Kimmelstiel et al 195)

Amyloidosis is a very rare complication of ulcerative colitis I have seen it only once Other morphological changes in the liver are listed in Table 69

In my experience viral hepatitis probably the homologous serum type is an important frequent and grave complication of ulcerative colitis It probably results from the frequent blood transfusions that are necessitated in some of these patients This is exemplified by a year-old man with ulcerative colitis who re

ceived a number of blood transfusions over a period of two months because of severe ulcerative colitis with intestinal hemorrhage. Six weeks after the last blood transfusion he developed jaundice and the other clinical and laboratory features of viral hepatitis. He died after a stormy downhill course lasting two weeks. At autopsy the liver was characteristic of acute yellow atrophy of fatal hepatitis (Fig. 42).

Another patient whom I followed for several years prior to his death and who was previously reported as a problem case of ileo colitis (Spellberg and Jackson) became markedly jaundiced several weeks before death. Clinically it was thought that this patient also had a homologous serum hepatitis acquired from the numerous blood transfusions. Morphologically, however, the marked fatty infiltration, diffuse fibrosis, bile duct proliferation resembled more an early nutritional cirrhosis. The rapidity of onset and rapid progression of jaundice along with marked round cell infiltration made it likely that a superimposed hepatitis was present. This patient was ill for some 10 years before death. His recurrent episodes were accompanied by fever, diarrhea, anorexia and loss of weight. He had several surgical procedures and had on several occasions developed a nutritional (hypoproteinemic) edema. This patient may have originally had a regional enteritis with subsequent colonic involvement. The combination of marked malnutrition and infection undoubtedly played the chief role in the hepatic damage.

Coexistence of Ulcerative Colitis and Liver Disease

When two chronic diseases such as cirrhosis and ulcerative colitis coexist it is not always easy to decide which condition preceded. Occasionally the clinical picture may be blurred so that a diagnostic problem may arise in making the following differentiation: 1. ulcerative colitis with secondary liver disease, 2. primary liver disease with secondary intestinal hemorrhage and 3. the coexistence of primary liver disease and ulcerative colitis with the liver disease preceding the colitis. The following case exemplifies this dilemma. A young man entered the hospital acutely ill. He was lethargic, had anorexia, a low grade fever and diarrhea containing gross blood. There was a history of infectious hepatitis about 1 year before with slow convalescence and continuous fatiguability. The liver was enlarged and somewhat tender and the spleen was palpable. The history of hepatitis definitely antedated the intestinal symptoms and it was surmised that the gastrointestinal bleeding was secondary to hypoprothrombinemia. Hypoprothrombinemia was not found but this did not rule out completely bleeding from increased capillary fragility.

The demonstration of a characteristic sigmoidoscopic and roentgenographic picture of ulcerative colitis proved the existence of this disease. There were periods of recrudescence of hepatic dysfunction which did not parallel the relapses of ulcerative colitis. The patient finally died in liver failure, and the morphologic picture of the liver was that of post necrotic cirrhosis. In this patient the liver disease antedated the ulcerative colitis. The ulcerative colitis was an added burden to the damaged liver leading to chronic hepatitis and the terminal cirrhosis.

Hepatic Dysfunction in Ulcerative Colitis

Hepatic injury in ulcerative colitis as deduced from abnormal liver function tests is even more common than morphologic alterations. Pollard and Block found some abnormal tests in 50% of their group of cases. This is much higher than the experience reported by Ross and Swarts. The abnormal tests include retention of bromsulfalein, positive flocculation tests, elevated alkaline phosphatase, elevated prothrombin time, and hypoproteinemia with reversal of albumin globulin ratio. Protein abnormalities are probably most frequently encountered. When this procedure is done by the salting out technique without fractionating the globulin the disturbance can be erroneously attributed to hepatic dysfunction. We have done electrophoretic studies of plasma of patients with ulcerative colitis and found a consistent depression of the albumin and elevation of the α_1 and α globulin. The beta globulin is occasionally slightly elevated while the gamma

globulin which is characteristically elevated in liver disease is normal in ulcerative colitis (Spellberg et al) (Table 70 and Fig 1b) This is not the electrophoretic pattern of hepatic disease Occasionally the gamma globulin was increased but this was the exception rather than the rule We believe that the protein disturbances in ulcerative colitis are independent of liver disease and are probably due to the malnutrition infection and loss of proteins from the intestine

TABLE 70

Electrophoretic Fractionation of Plasma Proteins in Patients with Ulcerative Colitis

P I	P I I C G	P I I P H
Albumin	26 96%	35 06%
Alpha Globulin	14 55%	16 50%
Alpha Globulin	16 38%	15 01%
Beta Globulin	16 07%	14 00%
Gamma Globulin	13 63%	1 84%
Fibrinogen Globulin	1 41%	12 55%

The flocculation tests are occasionally abnormal *but when we recollect that these de*pend on plasma protein abnormalities we should hesitate to attribute them solely to liver dysfunction Hypoprothrombinemia encountered in ulcerative colitis may occasionally be due to inanition coupled with inhibition of bacterial intestinal synthesis by orally administered antibiotics I have frequently seen rapid response of the prothrombin time to parenteral vitamin administration which is not usual in hepatic hypoprothrombinemia

Bromsulfalein retention of over 5% is frequently seen This abnormality is indicative of hepatic dysfunction usually caused by a fatty liver

The serum bilirubin is not elevated unless cirrhosis or hepatitis is superimposed on the ulcerative colitis Ross and Swartz found no jaundice in any of their patients and I encountered it only in those with severe liver disease referred to above

Regional Enteritis

All the factors contributing to hepatic injury in ulcerative colitis are also operating in regional ileitis and yet the literature is devoid of reference to this complication Crohn in his monograph on regional ileitis makes no mention of fatty changes in the liver or cirrhosis bromsulphalein retention of moderate degree marked alteration of serum proteins and severe depression of cholesterol levels can occur (Fig 89) I have seen fatty livers and nutritional cirrhosis at autopsy in patients dying from regional enteritis (p 514) I have noted fatty metamorphosis and focal hepatitis on needle biopsy in the living patient (Fig 89) Homologous serum hepatitis develops in some of these patients who receive numerous blood transfusions

Treatment and Prognosis

The first aim should be the prevention of hepatic injury in these grave intestinal maladies The treatment should be directed at the factors which are most likely to produce liver damage and this plan coincides with the direction which good treatment of the disease as a whole should follow An attempt should be made to

1 *minimize and control infection*
  maintain good nutrition
3 prevent hypoproteinemia
4 prevent blood loss and treat it with transfusion when it occur Toxic drugs have been mentioned as a possible cause of liver damage but the only toxic drugs that have been utilized recently in these diseases are the soluble sulfonamides These have been largely displaced by the newer antibiotic the hepatotoxic properties of which are minimal (Chapter 24) I am not aware of any evidence that non absorbable sulfonamides produce liver damage

A high protein intake should be enforced if need be by intravenous blood and plasma Vitamin supplements especially the B complex should be supplied in abundance and administered parenterally during acute phase because of possible malabsorption It is unfortunate that blood transfusions which should be used unhesitatingly in regional enteritis and ulcerative colitis because of their beneficial effect should increase the hazard of viral hepatitis (p 513)

The prognosis of coexistent liver disease and ulcerative colitis regardless of which disease develops first is much poorer than is the case

in either disease alone Hepatic disease in any chronically ill and malnourished individual is a serious problem and a patient with serious hepatic disease cannot withstand an added burden For these reasons the coexistence of these diseases calls for heroic measures and while the outlook is usually grave it is not necessarily hopeless

69 The Liver in Arthritis, Allergy, Neoplasms, and Other Conditions

The Liver in Gout

In the effort to determine the seat of the disturbed uric acid metabolism in gout the liver has been implicated It has been postulated that gout may result from a disturbance in some hepatic enzyme mechanism This problem of the relationship of gout to hepatic dysfunction has been thoroughly reviewed by Wolfson and associates and they present a comprehensive bibliography Their studies of hepatic dysfunction in gout lead them to the conclusions that uncomplicated gout shows a small percentage of abnormal tests while those with complications show abnormal tests in over one third of cases In the interval between attacks 2 5% of tests were abnormal in the acute and subacute gouty arthritis 11 7% and in the chronic gouty arthritis 13 1% of tests were abnormal It is further pointed out that the abnormal tests were largely those dependent on alterations in serum proteins that is the flocculation tests The elevation of gamma globulin may be due to extrahepatic cause The bromsulfalein alkaline phosphatase and cholesterol esters are only rarely deranged

The Liver in Other Types of Arthritis

Rheumatoid arthritis with its obscure etiology and resistance to therapy before the introduction of hormonal therapy was a fertile field for speculation In the search for a clue to the riddle of any disease suspicion may fall on the liver with its multitudinous functions It was suggested that the disturbance in some of the hepatic functions especially one of its detoxifying functions may eventuate in the development of rheumatoid arthritis This assumption became untenable when liver disease and jaundice was noted to cause amelioration of symptoms and a temporary arrest of the disease

The observations of the ameliorating effect of hepatic disease and pregnancy on the symptoms of rheumatoid arthritis led Hench and his coworkers to the discovery of the usefulness of cortisone and the adrenocorticotropic hormone in the treatment of this disease Hench noted that both hepatic and post hepatic (obstructive) jaundice produced a remission while hemolytic jaundice did not Hyperbilirubinemia produced by injection of bilirubin dehydrocholic acid mixtures had no effect Transfusions of blood from jaundiced patients likewise had no effect but the production of viral hepatitis by inoculation of serum obtained from patients with hepatitis resulted in improvement of symptoms in patients with rheumatoid arthritis Anicteric hepatitis was also observed to produce remissions of rheumatoid arthritis From all these observations



Fig 89 [illegible] (X [illegible]00) showing focal hepatic round cell infiltration and mild [illegible] fibrosis. This [illegible] had regional enteritis [illegible] and had [illegible] ments of [illegible] liver [illegible] at the time [illegible] 4.4 gm 100 cc Albumin 1 5 Globulin [illegible] 9 gm Serum bilirubin 0.1 mg 100 cc [illegible] 9 mg% [illegible] Cephalin cholesterol [illegible] BSP 14% [illegible] phosphatase [illegible]

the conclusion is inescapable that liver damage alters metabolism in a manner as to lead to the improvement of the arthritic symptoms.

Archer elaborated this theme and pointed out that all agents capable of producing remissions in rheumatoid arthritis are hepatotoxic agents and their action is dependent upon low grade liver damage. Among therapeutic agents used are gold salts, bismuth salts, hyperthermia and toxic doses of vitamin D; all these are potential hepatotoxic agents. Pregnancy is also capable of producing dramatic improvement of rheumatoid arthritis. The improvement during pregnancy has also been attributed to possible liver impairment. The dramatic improvement produced in rheumatoid arthritis by transfusing blood obtained from pregnant women suggests other possibilities. Similar hormonal imbalance in liver disease and pregnancy may be the basis of the effect on the joints. The increase of adrenal corticoids in the urine of patients with liver disease has been mentioned (p. 476). Some of these substances have a cortisone like effect on the arthritic joints.

While the existence of hepatic dysfunction as a cause of rheumatoid arthritis is not corroborated by the fact, hepatic dysfunction may accompany some cases of rheumatoid arthritis. Archer (1951) pointed out that previously reported data on hepatic dysfunction in rheumatoid arthritis were gathered after treatment and the toxic therapeutic agents rather than the disease were responsible for the hepatic damage. While this reasoning has merit, it should also be pointed out that rheumatoid arthritis with its prolonged fever, anorexia and inanition may result in liver damage. Positive flocculation tests were reported in some patients with rheumatoid arthritis (Kunkel 1948, Carter and Maclagan 1948). The elevation in serum globulin (Perlman and Kaufman) found in this disease may be of non hepatic origin and may be responsible for the altered flocculation reac

tions Other liver function tests however have been found abnormal in patients with rheumatoid arthritis (Hepburn et al 1943 and Rawls et al 1937 1939)

There is a scarcity of autopsy data in patients dying from rheumatoid arthritis as the principal diagnosis Rosenberg and coworkers studied 30 patients with rheumatoid arthritis who came to autopsy They found no major lesions involving the liver except in one patient who developed cinchophen hepatitis Several patients showed secondary amyloidosis of the liver and other organs The relationship of amyloidosis to rheumatoid arthritis is open to speculation It has been suggested that *amyloidosis in rheumatoid arthritis* may be secondary to prolonged vaccine therapy (Reimann and Ecklund) This explanation has merit since many of the reported cases of amyloidosis in rheumatoid arthritis received vaccine therapy (Chapter 71) However amyloidosis in rheumatoid arthritis has been observed before the era of vaccine therapy and there is no reason to suppose that rheumatoid arthritis which may run a chronic febrile course should not be capable of producing amyloidosis like other chronic infections

The Role of the Liver in Allergy

The relationship of the liver to allergic diseases may be divided into two categories 1 allergic disease or injury of liver and 2 the role of the liver in the pathogenesis of the allergic state

Allergic Diseases of the Liver (Allergic Hepatitis)

The end organs that give clinical expression to the allergic state are usually the ones containing smooth muscle However since vascular changes are important in allergic conditions, a phenomenon seen in the skin and nasal mucosa *the liver could show an allergic response* through alterations in its blood vessels In a sense amyloidosis is an allergic reaction since it is considered the result of an altered antigen antibody response to a foreign protein Amyloidosis is an uncommon entity The more classical forms of allergic response of the liver are even more rare if they occur at all in man

The antigenic substance in allergy is usually a protein and since the liver stands at the cross roads of the body s protein metabolism it is *surprising that it does not become sensitized* more often to one of the numerous proteins that are presented to it for construction reconstruction or repair

The freedom from allergic reactions extend to the entire gastrointestinal tract (except the tongue mouth and pharynx which in this respect may be considered part of the epidermis) which is remarkably free of proven allergic manifestations In spite of exhaustive studies attempting to correlate peptic ulcer and ulcerative colitis with some form of food allergy, most objective students of these problems are inclined to relegate allergy to a minor role

Isolated gastrointestinal allergy manifested by vomiting and diarrhea is a rare phenomenon *in my experience* Many individuals with altered physiology of the gastrointestinal tract due to emotional factors in their effort to reject the true etiology, persuade themselves and the unwary and indiscriminating physician that they are allergic to some food substance Indeed the time encrusted symptom of biliousness attempts to incriminate the liver and some food substance when the fault resides in the superego! I have seen only one proven case of *gastrointestinal* allergy to milk protein This was accompanied by abdominal pain nausea and diarrhea as well as gastroscopic changes in the gastric mucosa upon exposure to minute amounts of the offending protein (Spellberg and Baker) However the chief and clinically most important symptoms consisted of bronchospasms and violent asthmatic attacks A verified case of allergic peritonitis has been under my observation and several such cases have been described in the literature

If allergic manifestation of other abdominal viscera *are rare allergic hepatitis* is even more rare and can be relegated to the category of medical curiosity Urbach and Gottlieb in their comprehensive monograph on Allergy cite some older and chiefly foreign literature in support of this thesis of allergic hepatic injury The phenomenon of disturbed water and salt metabolism and hyperaminoacidemia *cannot* be accepted in themselves as proof of hepatic

dysfunction Right upper quadrant pain without evidence of organic disease has been frequently attributed to an allergic response of the biliary tract to an offending food This usually refers to the extrahepatic biliary tree Some of the observations upon which this is based and cited by Walzer and associates may be open to question However these workers demonstrated an allergic response in the gall bladder of the Rhesus monkey by passively sensitizing this organ to cottonseed protein A subsequent intravenous injection of this protein resulted in edema hyperemia and increased mucus secretion of the gall bladder Histologic examination revealed edema with cellular infiltration consisting of eosinophiles How the intact human gall bladder may become sensitized is not easy to deduce from these experiments but presumably in allergic individuals may show sensitization of even well protected organs

An allergic type of focal necrosis of the liver has been produced in rabbits by sensitization with crystalline egg albumin The final reaction was produced by injecting the allergen intraperitoneally or into the mesenteric veins (Hartley and Lushbaugh) Such allergic hepatic necrosis has not been to my knowledge reported in man Jaundice occasionally reported to develop on an allergic basis can be more logically explained on the basis of edema or spasms around the sphincter of Oddi The existence of a true allergic hepatitis in man has not been proven

The Role of the Liver in the Pathogenesis of the Allergic State

Since the liver is charged with the responsibility of filtering the products of protein absorption coming from the intestines and converting them into proteins or amino acid combinations needed by the body it becomes easy to visualize that a disturbance of this function may result in the introduction of proteins foreign or deleterious to the organism and capable of acting as a sensitizing antigen Both dysfunction (Shay et al) and hyperfunction (Lelner and Waldman) of the liver has been held responsible for the allergic mechanism The implication of the liver in the allergic phenomenon dates back to 1910 when Manwaring noted that the pronounced hypotension in canine anaphylactic shock was due to liberation of a depressor substance by the liver Over a quarter of a century later Dragstedt and Mead (1936) demonstrated that this depressor substance is histamin It is known that histamin can be liberated by most tissues but Manwaring and his associates concluded from their experiments on dehepatized (Eck Fistula) dogs that the liver is the chief source of this substance The role of the liver in irreversible traumatic shock in which (VDM) vasodepressor substance is liberated (p 485) directs one's attention to this substance in addition to histamin as the cause of the hypotension

The prolongation of the clotting time and the formation of an anticoagulant in anaphylactic shock of dogs was demonstrated by Wolf and later by Weil The liver was thought to be the source of this substance and later it was demonstrated that this substance is heparin liberated by the liver (Jaques and Waters) These observations indicate that the liver is profoundly disturbed in anaphylactic shock and that some of the grave physiological abnormalities in anaphylactic shock are secondary to hepatic disturbance They do not convey the impression that the liver is the sole responsible organ in anaphylaxis or that the liver dysfunction precedes or antedates the anaphylactic reaction It certainly does not suggest even obliquely that the liver is responsible for the clinical type of allergy that we see daily

There is a difference of opinion as to the type of hepatic disturbance associated with the allergic state Several allergic patients observed by Shay and coworkers responded to decholin and one to cholecystectomy The improvement was attributed to correction of hepatic dysfunction by these measures The relief of arthritic symptoms following the development of urticaria reported by Rawl suggests that hepatic dysfunction may have caused the urticaria and resulted in the well known ameliorating effect on the arthritis On the other hand Lelner and Waldman (1952) suggest that hyperfunction of the liver may be responsible for allergy or hypersensitivity The favorable effect of decholin on allergic states

tions Other liver function te l been found abnormal in p tie toid arthritis (Hepburn Rawls et al 1937 ...

There is a scarcity ... tients dying from ... or principal diagno ... of the liver studied 50 patie ... who came t ... the mode of action of these lesions inv ... would lead us tient wh ... al medicine but there is more convincing Several ... action is more direct than of the ... of liver function Decholin of ... similarity to cortisone may t ... effect in the body and ... the symptoms of allergy ... Mallen studied the plasma ... liver function in 56 allergic pa ... The liver function tests used included ... excretion hippuric acid ... alkaline phosphatase level They ... deviation of the plasma proteins or ... other tests to indicate that hepatic dis ... plays a role in the allergic state The ... liver may have some subtle relationship to ... allergic phenomenon but such assumption is entirely speculative and unproven At the present time there is no acceptable evidence that the liver plays a direct etiologic role in the production of clinical allergy

The Role of Liver in Allergy—Summary

1 **Resynthesis of proteins from the gastrointestinal tract**
2 **Anaphylactic shock**
   a **depressor substances liberated by liver (histamin) (VDM)**
   b **anticoagulant liberated by liver (heparin)**

The Liver in Malignant Neoplasms

The tendency of the liver to attract meta static carcinoma has been discussed (Chapter 18) There appears to be a tendency for the liver to undergo functional and morphological changes in patients suffering from carcinoma of the gastrointestinal tract This has been studied intensively by the group from the Memorial Hospital of New York (Ariel et al and Abels et al) These workers have found hypoproteinemia and especially hypoalbuminemia in the majority of patients with gastrointestinal malignant tumors Plasma vitamin A levels were depressed and other evidence of functional abnormality were obtained This New York group also studied the chemical composition of the livers of some of these patients and found increased amounts of fat and probable decreased amount of glycogen and proteins

The effect of extrahepatic neoplasms on liver catalase in animals has been recently reviewed by Greenstein (1952) Liver catalase invariably decreases when the animal is inoculated with a rapidly growing tumor and the catalase promptly returns to normal with extirpation of the tumor It has been further noted that an extract of human cancer as well as mouse tumor referred to as toxohormone when injected into animals resulted in a drop in liver catalase The activity of ' toxhormone can be neutralized by the injection of iron salts and therefore it is postulated that this material produces its effect by depriving the liv ... required for the synthesis of ca ... observations reemphasize the ... in which the liver is affected by ... logic processes in the body

Disturbances in liver function are secondary to the prolo ... that is frequently entailed in advanced cancer anywhere but e ... gastrointestinal tract Interferer ... tion is due to the accompanyi ... pain vomiting and disturba ... action I have yet to see depressi ... albumin or significant disturbance function in patients with malignan ... who maintain their weight and state

Bromsulphalein retention and the serum alkaline phosphatase ... metastases to the liver and this been confirmed by surgery or ... albuminemia and hypo ... hepatic dysfunction and increased The administration of a high ... carbohydrate diet with parenteral tation is usually effective in abnormalities The use of lipotropic

speed up the process if fatty metamorphosis is suspected and may be worth using if time is essential If the carcinoma is far advanced it may be impossible to elevate the serum albumin even with repeated plasma and blood infusions The maintenance of the patient s circulation nutrition and minimizing infection are all important All the methods used in the treatment of chronic liver disease should be implemental here Testosterone propionate has been used to reverse the nitrogen loss in these patients and this hormone has also been recommended for patients with chronic liver disease (Cooper et al 1951)

The cirrhotic liver is less frequently the site of metastatic carcinoma than is the normal liver (p 4-7)

The Liver in Diseases of the Central Nervous System

The relationship between disease of the liver and brain disease is discussed in Chapter 74 Disease and injury of the spinal cord seems to result in damage and functional impairment of the liver Thompson and Rice found hepatomegaly in 33 of 50 paraplegic patients but since the degree of enlargement was not specified nor were functional studies made the significance of this is uncertain However they found amyloidosis in four autopsied patients with paraplegia and two of these had hepatic amyloidosis Cooper and his associates reported a series of observations dealing with the involvement of the liver in patients with spinal cord injury Gynecomastia has been observed following injury to the spinal cord but this has not been definitely correlated with hepatic dysfunction

The most recent study by Cooper and associates (1951) of hepatic function in eight patients with spinal cord injury resulting in paraplegia showed abnormalities in six Bromsulfalein retention was marked from 6 to 40% after 60 minutes This gradually returned to *normal within 10 weeks in all but one of these* patients Mild elevation of the serum bilirubin including the direct reacting fraction occurred in four an abnormal cephalin cholesterol flocculation was noted in one and the cholesterol and cholesterol esters were depressed in the same patient A negative nitrogen balance and increased protein catabolism was evidenced by increased nitrogen excretion in the urine and depression of the serum protein

The pathogenesis of hepatic damage following spinal cord injury is not clear but is probably dependent upon a combination of factors The increased protein catabolism and gynecomastia are in part related to the liver dysfunction but other factors are contributory Nonspecific effects of injury such as shock and blood loss contribute to the hepatic injury That these are not the only factors is evidenced by the prolongation of the functional impairment as well as by the greater impairment after spinal cord injuries as compared with other serious injuries The reaction to acute stress along the lines of the general adaptation syndrome outlined by Selye is known to be accompanied by increased nitrogen catabolism as well as by liver injury The stressful stimulus of spinal cord injury may be greater than is the case in other injuries and the hypotensive effect of high spinal cord lesions are likewise more marked because of involvement of the vasomotor apparatus The great general incapacity that accompanies paraplegia leads to malnutrition and infection These in turn will result in liver impairment

The prevention and treatment of all the elements that hasten the patient s disintegration are also essential in the treatment of hepatic dysfunction in these grave injuries

The Role of the Liver in Dermatological Conditions

In dermatological conditions that are clearly dependent upon systemic disease the liver is frequently involved In this group there are systemic infections with hepatic involvement such as syphilis and are discussed under the appropriate heading The collagen diseases lupus erythematosus disseminatus periarteritis nodosa and dermatomyositis not infrequently show hepatic involvement An attempt has been made to implicate the liver in other dermatologic conditions in which the pathogenesis and etiology is obscure So-called congestive eczema or stasis dermatitis in which no

obvious gross circulatory abnormalities are detectable has been thought to depend upon hepatic dysfunction (Eichenlaub and Osbourn) Griffith and Baumeister performed liver function tests on several patients with stasis dermatitis and found no significant deviation from the normal

In chronic liver disease accompanied by ascites and edema changes in the edematous skin may be expected These changes would probably result from the mechanical effect of the excessive fluid accumulation rather than from some subtle biochemical disturbance Liver disease per se is devoid of changes in the skin except for those secondary to jaundice the pigmentation in hemochromatosis the spider naevi and telangiectasis palmarerythema and changes due to infection and avitaminosis

70 — *The Effect of Surgery on the Liver and Abnormal Liver*

In a discussion of the effect of surgery on the liver consideration must be given to the effect on the abnormal as well as normal liver There is an abundance of evidence that even minor surgical procedures augment the damage of the abnormal liver occasionally to a catastrophic degree The outcome of surgery on a patient with hepatic disease is characterized by its unpredictability Minor operations may end fatally A patient with cirrhosis of the liver may die after laparotomy and surgical biopsy (p 556) This may happen in the face of relatively normal liver function tests On the other hand many patients with cirrhosis have been subjected to the prolonged surgery entailed by the shunting procedures without apparent deleterious effects (Chapter 50 p 360) Patients with tuberculosis and amyloidosis of the liver have been shown to be only a slightly greater surgical risk than patients with tuberculosis without amyloidosis (Auerbach and Stemmerman 1946)

Because of the unpredictability of the outcome and the greater risk involved in operating on patients with parenchymatous liver disease I am opposed to surgery in such individuals Even exploratory laparotomies may end disastrously No elective surgery should be performed in such patients unless the withholding of surgery would involve a greater risk than that of the surgical procedure *Porta caval* shunts fall into this category when death from exsanguinating hemorrhage is threatened And even in this situation certain patients are excluded because of the severity of the hepatic involvement Emergency procedures such as appendectomy have to be carried out in spite of the risk Cholelithiasis complicating liver disease presents a challenge to the clinician and is discussed on page 426 The variability of the outcome of surgery in patients with liver disease may depend upon the type of hepatic involvement and the dynamics of the process That is if the process involves chiefly the parenchymal cells rather than the supporting structures the response to surgery is poor Likewise if the process is progressive the prognosis is poor since the progression is hastened by surgery While if the process is stationary or regressive the response to surgery

may be good. This concept may explain why many patients with bleeding esophageal varices survive surgery for portal hypertension without immediate deleterious results. As is pointed out in Chapter 49, esophageal varices and portal hypertension may exist with minimal hepatocellular damage.

Prognostic Signs and Symptoms

Some signs, symptoms, and laboratory tests may give a clue to the category of liver disease and help the proper evaluation of the particular case in so far as prognosis to surgery is concerned. Patients with fetor hepaticus, progressive jaundice, central nervous system disturbances, and hemorrhagic phenomenon are poor surgical risks. This is likewise true of individuals with a low serum albumin below 3 gm%, a high prothrombin time, and marked bromsulfalein retention. A high and rising thymol turbidity test, as well as progressively increasing cephalin-cholesterol flocculation test should make one uneasy about performing surgery.

The measures to be taken to minimize damage to the liver when surgery is imperative will be detailed below.

Normal Liver

There is an abundance of evidence that the normal liver is also damaged by surgical procedures but the damage is mild and transient. The damage may be attributed to one of the following factors:

1. anaesthesia
2. trauma of surgery
3. blood loss (shock)
4. inanition

Anaesthetic Agents

The hepatotoxic effect of various anaesthetics has been referred to in Chapter 4. Chloroform, the most hepatotoxic of all anaesthetic agents, no longer presents a problem because of the rarity with which it is used. Anoxia may play a role in the hepatotoxic action of some of the inhalation anaesthetics. The protective effect of oxygen on the liver was demonstrated with the use of chloroform and divinyl ether (vinethene) (Goldschmidt et al.). These experiments were performed on the dog, and in this animal diethyl-ether was also shown to be capable of producing hepatic damage. Not only oxygen but a high carbohydrate diet prior to exposure also had a protective effect on the liver.

Schmidt and coworkers studied the reaction of the liver to various operations by means of the hippuric acid synthesis test. A variety of surgical procedures were involved, and the anaesthetic agents included ether, avertin, novocain infiltration, and spinal anaesthesia. They concluded that both ether and avertin produced a significant decrease in hippuric acid synthesis while spinal anaesthesia resulted in no depression of liver function with the exception of two patients who had a marked drop of blood pressure during anaesthesia. Patients on whom local infiltration anaesthesia was used plus morphine and amytal preoperatively likewise escaped changes in liver function. However, these operations were not as extensive as the ones in which the other anaesthetic agents were used.

The anaesthetic agent is not the major determining factor in post-operative liver damage. This is brought out by more recent observations. Geller and Tagnon made observations in patients who were given nitrous oxide, oxygen and ether, spinal anaesthesia alone, and spinal anaesthesia plus thiopental (pentothal) sodium and found no difference in the alteration of the liver function tests. French and coworkers found no difference between ether and cyclopropane in their effect on the liver.

Anoxia

Since anoxia is known to injure the liver and is an important factor in anaesthetic injury, it follows that anoxia induced by other means can act in the same manner. Thus anoxia can result from blood loss, shock, or rapid drop in blood pressure. The injurious effect of spinal anaesthesia may be in part explained by drop in blood pressure. Spinal anaesthesia has been shown to result in a drop in arterial oxygen saturation. Shock from surgical trauma or loss of blood may likewise in hepatic anoxia and damage this vital

Moreover liver anoxia may result in increased discharge of VDM and increase the drop in blood pressure

Surgical Procedures

The degree of surgical trauma as determined by the type, extent and duration of the surgical procedure has an important bearing on liver damage Keeton and associates found hepatic dysfunction more marked after cholecystectomy than after herniorrhaphy The group from Memorial Hospital found hepatic disturbance more marked in the patients with intraabdominal procedures (Geller and Tagnon) as compared with extra abdominal procedures (Tagnon et al) However they saw no difference between their various abdominal operations all of which were of major degree

Preceding hepatic injury undoubtedly plays a role in the degree of postoperative impairment Therefore the disease for which surgery is done may have a bearing on the preoperative liver damage This view point is emphasized by French and associates who found the least postoperative hepatic dysfunction after gastrotomies slightly more after cholecystectomies and most damage after surgery for portal hypertension However there is no uniformity of opinions as to which surgical diseases and procedures are most likely to result in hepatic dysfunction Engstrand and Friberg found little effect on the liver from cholecystectomies and cholecystostomies done under spinal anaesthesia while gastric resection done with the same anaesthetic and proper precautions against anoxia resulted in prolonged depression of hepatic function

Malnutrition

The nutrition of the patient plays a role in the postoperative hepatic injury as it does in other types of hepatic disease That the preoperative nutritional state of the patient is important in the postoperative course is obvious and requires no restatement The postoperative period of inanition is likewise an important factor in disturbing hepatic function This was brought out by the extensive and well controlled studies of Keeton and his associates They found that a high caloric high protein diet (~6 gm protein kilo) forcibly administered resulted in a positive nitrogen balance and reduction of postoperative urobilinogenuria

Fever

Fever which may be due to infection or absorption of traumatized tissue undoubtedly has an added effect in producing liver damage The effect of fever and infection on the liver is discussed in Chapter 25 The more serious and more extensive operations are apt to be accompanied by the most prolonged and highest febrile reaction The fever acts synergistically with the other factors described above since demand for oxygen and food stuffs is increased with elevation of temperature

Laboratory Evidence of Liver Damage

The following tests have been utilized and found abnormal postoperatively

- serum bilirubin
- urine urobilinogen
- bromsulfalein excretion
- hippuric acid synthesis
- thymol turbidity and
- cephalin cholesterol flocculation
- serum cholesterol and cholesterol esters
- serum proteins

A rise in serum bilirubin is not an infrequent sequel to cholecystectomy and may be due to transient edema of common duct or spasms of the sphincter of Oddi 19 of 33 patients studied by Geller and Tagnon showed postoperative rise in serum bilirubin of 0 3 mg or more None of these had cholecystectomies however all but one had blood transfusions The increase in bilirubin was slight in most instances and did not exceed the normal levels of 1 0 mg in some of these patients The bilirubin increase was undoubtedly related to increased production (prehepatic) from the administered blood and decreased excretion from hepatocellular damage (hepatic) Others have found an occasional mild rise of serum bilirubin following abdominal operations (French et al 1951 Zamcheck et al 1949 Engstrand 1945) Although the administration of blood is not specifically mentioned it is assumed that most patients undergoing major abdominal surgery in this era are given the benefit and subjected to the hazards of blood transfusion The serum

bilirubin elevation is most frequently noted on the first postoperative day and rarely appears after the third day

Urobilinogen excretion in the urine increases postoperatively and reaches the maximum excretion by the third postoperative day (Keeton et al) This is more marked after more extensive operations (cholecystectomy) as compared with less traumatic operations (herniorrhaphy) The administration of blood transfusions would induce increased urobilinogen excretion Keeton and coworkers noted a marked increase in excretion of this pigment with onset of infection and the ability of high protein diets to reduce hyperbilirubinuria

Bromsulphalein retention has been noted postoperatively by various observers The abnormality is most marked on the first postoperative day and gradually returns to the preoperative level about the 6th postoperative day This test is the most frequent one to deviate from normal after surgery The retention varies with the type of operation and is increased by fever and infection Retention of 64% at 45 minutes was noted after gastrectomy (French et al)

Hippuric acid synthesis has been reported to become abnormal in earlier reports (Schmidt et al 194-) but since this test is not widely used at the present time it is not mentioned in the more recent literature

Cholesterol alterations of minor degree can occur postoperatively but this is not a sensitive test for this type of injury

Prothrombin time increases uncommonly after surgery and the changes that occur are minor It has been pointed out that an occasional patient will show a decrease of prothrombin time after surgery performed under spinal anaesthesia (Keeton et al Borgstrom 1943)

Alkaline phosphatase in the serum has been noted to fall immediately postoperatively with a subsequent rise on the 5th to 6th day to definitely abnormal levels

Serum protein alterations of minor degree have been noted (Keeton et al) These are not marked in patients without definite preoperative liver damage The flocculation tests usually remain unaltered although mildly positive cephalin cholesterol flocculation tests (2+ and 3+) have been noted (Geller and Tagnon)

Liver biopsy with specimens obtained immediately on opening the abdomen and at the termination of the operation has shown definite alteration of structure (Zamchek et al) This rapid change in structure in the brief time of the operation is extremely interesting and should be a warning to those who rely on surgical biopsies The changes noted included

1 capsular and subcapsular inflammation
  aggregation of neutrophiles chiefly around the central veins and
3 parenchymal cell necrosis

71— Amyloidosis of the Liver

Hepatic amyloidosis is not an important entity from the point of view of frequency but it is interesting because of its obscure pathogenesis and the chemical peculiarities of the amyloid substance or substance Amyloidosis is usually divided into the following four groups

1 primary amyloidosis
  secondary amyloidosis
3 amyloidosis due to multiple myeloma
4 isolated amyloid tumors

It may be proper to divide all cases of amyloidosis into primary and secondary depending upon whether some definite etiologic agent

Moreover liver anoxia may result in increased discharge of VDM and increase the drop in blood pressure

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urine urobilinogen
bromsulfalein excretion
hippuric acid synthesis
thymol turbidity and
cephalin cholesterol flocculation
serum cholesterol and cholesterol esters
serum proteins

A rise in serum bilirubin is not an infrequent sequel to cholecystectomy and may be due to transient edema of common duct or spasms of the sphincter of Oddi 19 of 33 patients studied by Geller and Tagnon showed postoperative rise in serum bilirubin of 0 3 mg or more None of these had cholecystectomies however all but one had blood transfusions The increase in bilirubin was slight in most instances and did not exceed the normal levels of 1 0 mg in some of these patients The bilirubin increase was undoubtedly related to increased production (prehepatic) from the administered blood and decreased excretion from hepatocellular damage (hepatic) Others have found an occasional mild rise of serum bilirubin following abdominal operations (French et al 1951 Zamcheck et al 1949 Engstrand 1945) Although the administration of blood is not specifically mentioned it is assumed that most patients undergoing major abdominal surgery in this era are given the benefit and subjected to the hazards of blood transfusion The serum

bilirubin elevation is most frequently noted on the first postoperative day and rarely appears after the third day

Urobilinogen excretion in the urine increases postoperatively and reaches the maximum excretion by the third postoperative day (Keeton et al) This is more marked after more extensive operations (cholecystectomy) as compared with less traumatic operations (herniorrhaphy) The administration of blood transfusions would induce increased urobilinogen excretion Keeton and coworkers noted a marked increase in excretion of this pigment with onset of infection and the ability of high protein diets to reduce hyperbilirubinuria

Bromsulphalein retention has been noted postoperatively by various observers The abnormality is most marked on the first postoperative day and gradually returns to the preoperative level about the 6th postoperative day This test is the most frequent one to deviate from normal after surgery The retention varies with the type of operation and is increased by fever and infection Retention of 64% at 45 minutes was noted after gastrectomy (French et al)

Hippuric acid synthesis has been reported to become abnormal in earlier reports (Schmidt et al 1942) but since this test is not widely used at the present time it is not mentioned in the more recent literature

Cholesterol alterations of minor degree can occur postoperatively but this is not a sensitive test for this type of injury

Prothrombin time increases uncommonly after surgery and the changes that occur are minor It has been pointed out that an occasional patient will show a decrease of prothrombin time after surgery performed under spinal anaesthesia (Keeton et al Borgstrom 1943)

Alkaline phosphatase in the serum has been noted to fall immediately postoperatively with a subsequent rise on the 5th to 6th day to definitely abnormal levels

Serum protein alterations of minor degree have been noted (Keeton et al) These are not marked in patients without definite preoperative liver damage The flocculation tests usually remain unaltered although mildly positive cephalin cholesterol flocculation tests (2+ and 3+) have been noted (Geller and Tagnon)

Liver biopsy with specimens obtained immediately on opening the abdomen and at the termination of the operation has shown definite alteration of structure (Zamchek et al) This rapid change in structure in the brief time of the operation is extremely interesting and should be a warning to those who rely on surgical biopsies The changes noted included

1 capsular and subcapsular inflammation
2 aggregation of neutrophiles chiefly around the central veins and
3 parenchymal cell necrosis

71 — *Amyloidosis of the Liver*

HEPATIC amyloidosis is not an important entity from the point of view of frequency but it is interesting because of its obscure pathogenesis and the chemical peculiarities of the amyloid substance or substances Amyloidosis is usually divided into the following four groups

1 primary amyloidosis
secondary amyloidosis
3 amyloidosis due to multiple myeloma
4 isolated amyloid tumors

It may be proper to divide all cases of amyloidosis into primary and secondary depending upon whether some definite etiologic agent

is found and place the amyloidosis of multiple *myeloma into the secondary group*. However the organ distribution of the multiple myeloma amyloidosis is similar to the distribution of the primary type. The isolated amyloid tumors may be either primary or secondary. There are some chemical differences between the various types of amyloid.

Types of Amyloidosis

Primary amyloidosis occurs in the absence of any specific preceding disease. The organs that it usually involves are the tongue, the skin, the myocardium, and the gastrointestinal tract, while the liver, kidneys and spleen are less commonly and more sparsely involved. It should be therefore of less interest here, but cases of primary amyloidosis with marked involvement of the liver have been reported. The affinity of this amyloid for various substances and dyes *is erratic*. Congo red which is almost always picked up by the secondary amyloid is picked up erratically by the primary amyloid.

Secondary amyloidosis occurs after prolonged infections and suppurations, especially tuberculosis and chronic osteomyelitis. It may occur after other prolonged and debilitating infections and neoplastic diseases. The organs which commonly attract this amyloid deposit are the liver, kidneys, spleen and adrenals; other organs may be involved to some degree. These deposits stain vividly with congo red, iodine and crystal violet.

Amyloidosis of multiple myeloma, although secondary to a known disease, shows the distribution and unpredictable staining characteristics of the primary variety.

Amyloid tumors are usually solitary but may be multiple. They may be situated in the larynx, urinary bladder, tongue, bones and eye. They may be primary or secondary in etiology and vary in their staining characteristics. I am not aware that they have been described in the liver.

Pathology

The gross findings vary with the type of amyloid disease. Thus in the secondary type the causative suppurative disease is found. Likewise the organs involved differ as pointed out above. The severity of hepatic involvement is greater in the secondary amyloidosis, but the liver has been found markedly *involved in primary amyloidosis*. The involvement of the tongue and the entire gastrointestinal tract with the occasional formation of gastric ulcers are interesting findings in the primary disease.

The liver is enlarged, the exact size depending on the degree of involvement. It may exceed 4000 gm in weight and in one patient the liver weighed 5,700 gm. It is firm in consistency, but it is rubbery rather than hard. It has a translucent waxy appearance. The cut surface invariably stains a mahogany brown with iodine in secondary amyloidosis. In primary amyloidosis the staining characteristics vary.

Microscopically, the amyloid material is seen deposited between the endothelial cells of the sinusoids causing compression and atrophy of the parenchymal cells. The distribution of this material is widespread and is greater in quantity in the secondary disease. In primary amyloidosis, the amyloid deposit is apt to be most marked intra- and perivascularly in the larger portal vessels. The deposits in these vessels begin in the media and extend in both directions. The amyloid material usually stains distinctly with metachromatic aniline dyes, congo red and iodine. The metachromatic aniline dyes, including gentian violet, methyl violet, methylgreen and crystal violet, give it a red tinge on heating. Congo red gives it a brilliant pink. Iodine gives it a brown color and an almost black mahogany brown when dilute sulfuric acid is added *(Table 71)*.

In the secondary amyloidosis all the stains are absorbed, but the primary disease may stain with only one of these and not the others. Giant cells occur in the region of amyloid deposit.

Nature and Pathogenesis of Amyloid

Amyloid is a protein carbohydrate complex. The carbohydrate fraction is a polysaccharide which is responsible for the staining reaction to iodine. Its relationship to starch is expressed in the term amyloid. The fact that not all amyloid is identical chemically is evident from its variation in staining characteristic. The

Table 71

Color Reactions of Amyloid to Various Dyes

Dye	*Color*
Gentian Violet	Red Tinge
Methyl Violet	Red Tinge
Methyl Green	Red Tinge
Crystal Violet	Red Tinge
Congo Red	*Brilliant Pink*
Iodine	Brown
Iodine + Dil. H_2SO_4	Black or Mahogany Brown

secondary amyloid may be more uniform since it invariably produces the staining reaction with the substances enumerated (Table 92). Secondary amyloid may stain characteristically with all these stains but invariably stains with one of them. There is no way of predicting which of the dyes will be absorbed by it. The absence of reaction to iodine suggests the possible absence of a carbohydrate fraction in some of the primary amyloid while its occasional staining with lipid stains (Koletsky and Stecher) suggests the presence of fat.

The occurrence of secondary amyloidosis in chronic infections suggests that the material forms in response to a bacterial toxin or foreign protein. Bailey (1916) successfully produced amyloidosis experimentally by injecting dead or living bacteria or bacterial toxins. Kuczynski (19[illegible]) was the first to produce amyloidosis in mice by the injection of sodium caseinate. Jaffe (19[illegible]6) extended the experiments and produced amyloidosis by injecting foreign serum as well as sodium caseinate. These experiments bring up the question of an allergic reaction to a foreign protein in the form of an antigen antibody reaction. It has been suggested that this reaction occurs between one of the serum globulins and fixed elements in the vascular wall resulting in a precipitation of this peculiar material (Koletsky and Stecher).

Incidence

Amyloidosis in general is a rare condition and the hepatic involvement is even less common since not in all patients is the liver involved. Primary amyloidosis is much less common than the secondary; only about 50 cases have been reported in the literature. While the liver involvement is infrequent in this group it does occur and has to be considered in the differential diagnosis of hepatic enlargement. Of the forty six cases of primary amyloidosis reviewed by Eisen (1946) 8 or 17% had hepatic involvement.

Secondary amyloidosis is not common but it is not nearly as rare as the primary variety. Moschkowitz found 4[illegible] autopsied cases with amyloidosis in [illegible]0 years at Mount Sinai of New York. Rosenblatt found a [illegible]7% evidence of amyloidosis in 1727 consecutive autopsies while Saleeby found the incidence in his autopsies series to be only 1.7%. A more recent report from Montefiore Hospital in New York shows 10[illegible] cases of amyloidosis among [illegible]60 autopsies (Orloff and Felder). 78 cases of amyloidosis were found in 1[illegible],000 consecutive autopsies at Bellevue (Spain and Riley). The liver was involved in approximately 60 of these cases. Hepatic involvement in amyloidosis secondary to multiple myeloma is least common and occurs in about 6% of cases.

Clinical Manifestation

In the secondary amyloidosis the primary disease overshadows the amyloidosis and the hepatic findings. Primary amyloidosis is most common in older individuals while secondary amyloidosis has the highest incidence in a younger age group similar to that of tuberculosis, usually between [illegible]0 and 40.

The liver is enlarged, occasionally reaching down to the iliac crest. The organ is smooth, firm but not hard, nor tender. The spleen is involved very commonly (over 80%) in secondary amyloidosis and therefore this organ is frequently palpable. The splenic enlargement can occur in chronic infections independently of amyloidosis and hepatic enlargement in chronic tuberculosis may raise the question of hepatic tuberculosis.

Jaundice is so rare in secondary amyloidosis that it has been claimed to be absent in this type of hepatic involvement. However several cases of jaundice in this condition have been reported (Spain and Riley and Taber et al.). Jaundice seems to be more common in primary amyloidosis since three cases with jaundice were reported within 3 years (Orloff and Felder 1946, Zetzel 1947 and Berris and Wolff 1949). The jaundice in these cases was mild in two and marked in one. The pathogenesis of the jaundice is on the basis of compression of bile canaliculi by the amyloid deposits and the concomitant atrophy of the hepatic cells.

Ascites and edema are frequently present when the disease involves the liver and spleen. In primary amyloidosis ascites is more common than hepatic involvement and may be due to cardiac involvement. Edema, dyspnea and hydrothorax also occur as sequelae to myo

cardial amyloidosis Ascites occurring in pulmonary tuberculosis must be differentiated from tuberculous peritonitis

Gastrointestinal hemorrhage is a serious but rare occurrence in amyloidosis Primary amyloidosis with gastrointestinal involvement may result in gastric ulceration Hemorrhage has been reported in the absence of gastrointestinal ulceration (Berris and Wolff) Hypoprothrombinemia along with vascular damage from amyloid deposits are probably the other responsible factors Other types of hemorrhage such as ecchymosis petechiae oozing from gums and mucous membranes of mouth are noted

Urinary symptoms such as polyuria and nocturia are expressions of renal amyloidosis and are seen in the secondary type of disease It is noteworthy that renal amyloidosis is accompanied by a normal blood pressure

Laboratory Features

The Congo red test when positive is considered specific for amyloidosis It is not always positive however It may be negative in amyloidosis for two reasons 1 the particular amyloid material does not absorb the dye this is especially apt to occur in the primary disease and 2 the amyloid deposits are not extensive enough to absorb all of the amyloid injected In hepatic amyloidosis the deposits are of sufficient magnitude to produce a positive Congo red test if the disease is of the secondary type Therefore a diagnosis of secondary amyloidosis is unjustified in the face of a negative Congo red test

The Congo red test is performed according to the Taran and Eckstein modification of the original Benhold technique

1 1 cc of 1% aqueous solution of Congo red per 10 lbs of body weight is injected intravenously
2 10 cc of blood is obtained by vena puncture 4 minutes and 1 hour after the dye administration This should be obtained from a vein other than the one into which the injection is made
3 The blood is allowed to clot and centrifuged
4 The serum is removed by pipette and placed into graduated centrifuge tubes
5 Acetone equal in amount to the serum is added to each of the tubes the contents shaken
6 The contents of these tubes are again centrifuged and the supernatant clear fluid is poured off without agitation
7 The clear supernatant fluid from each of the tubes is compared in a colorimeter
8 The 4 minute sample represents 100% of the dye and the 1 hour sample represents the amount of dye remaining in the blood stream The difference between the two is the amount of dye absorbed by the tissues

What is a positive Congo red test? And are there false positive tests? Absorption of 90 to 100% of dye (that is disappearance of all but 10% or less of dye from serum) has been considered a positive test and an indication of amyloidosis The test has fallen into disrepute because of an occasional false positive test Selikoff has recently reviewed the merits of this test and came to the following conclusions

1 Negative test 0–89% dye absorption
2 Suggestively positive test 90–99% dye absorption
3 Probably positive 100% absorption
4 Definitely positive 90–100% absorption on two consecutive tests

These conclusions are derived from the experience that occasionally even a 100% absorption may show a drop below 89% on subsequent testing Such a patient has been found anatomically free of amyloidosis Selikoff claims that no patient who has had two consecutive positive tests (90% absorption or more) has been found free of amyloid or has shown a reversal of the test and therefore two positive tests is conclusive proof of amyloidosis It has been shown in animal experiments that amyloid can be resorbed and disappear, especially from the liver There is evidence that amyloidosis in man may decrease and even disappear A reversal of a positive test may therefore be a sign of improvement unless the interval is too brief

Biopsy of the liver is of course the ideal method of proving the presence of hepatic amyloidosis Special stains should be applied to the tissue for mild amyloid deposits may be missed with routine hematoxylin and eosin stains Hepatic amyloidosis has been diagnosed

by needle liver biopsy Biopsy of the gums has been suggested as a means of diagnosing secondary amyloidosis since this tissue is frequently involved Absence of amyloid from the gums does not rule out amyloidosis

Liver function tests do not show marked changes except in exceptional instance Serum bilirubin elevation is rare and usually mild When hyperbilirubinemia occurs the prompt reacting fraction is elevated In one patient a serum bilirubin of 16 3 mg has been recorded (Orloff and Felder) This patient also showed an elevation of the alkaline phosphatase to 76 6 Bodansky units suggesting intrahepatic biliary obstruction Bilirubinuria as well as urobilinogenuria occurs

The plasma proteins are decreased but there is usually no disproportion in the decrease of the two fractions and the ratio between albumin and globulin remains the same In keeping with the slight protein disturbance the flocculation tests are either mildly positive or negative The Takata Ara reaction has been found positive in some patients with hepatic amyloidosis (Tiber et al) The thymol turbidity test is more frequently abnormal than the cephalin cholesterol flocculation test but few of these tests have been done in amyloidosis The cholesterol esters may be depressed and the total cholesterol may be elevated in the patients with marked hyperbilirubinemia It is curious that the prothrombin time has been elevated out of proportion to the hepatic dysfunction as evidenced by the other tests This depression of the prothrombin is not likely to be due to malabsorption of vitamin K since the biliary obstruction was not that severe It suggests rather that the metabolic disturbance entailed in amyloidosis may specifically interfere with prothrombin synthesis Mild bromsulfalein retention has been observed

Laboratory findings indicative of involvement of other organs are observed Albuminuria and cylindruria indicate involvement of kidney and electrocardiographic changes may appear because of myocardial amyloidosis

72 The Liver in Sarcoidosis and Tuberculosis

The Liver in Sarcoidosis (Besnier Boeck Schaumann s Disease)

Sarcoidosis like other granulomatous lesions syphilis (p 200) tuberculosis (p 2 2) and brucellosis (p 2 8) frequently attacks the liver The liver involvement by sarcoidosis can be missed easily unless looked for specifically This is evident from the rarity with which clinical involvement has been recorded as compared with the frequency of hepatic involvement at autopsy The clinical inconspicuousness of the hepatic involvement has resulted in the opinion that the tissues most commonly involved in this disease are the lungs lymph nodes skin bones and eyes The discrepancy in frequency of hepatic involvement between clinical and autopsy observations is emphasized by the cases reported by Ricker and Clark In this series the clinical incidence of hepatic involvement was 8 7% while the hepatic involvement at autopsy was 82%

Pathology

Sarcoidosis being a relatively benign disease offers few opportunities for post mortem studies up to 1952 slightly over 100 autopsied cases were reported In 1952 the literature was enriched by 3 autopsies reported by Gendel and associates and 30 reported by Longscope and Freiman The latter report included an extensive review of the literature as well

as a study of 160 additional clinical cases The findings at autopsy as well as the experience with needle biopsy has indicated that the liver is involved in 65 to 75% of cases and is the most commonly involved abdominal organ

Grossly the liver may be enlarged or normal in size depending upon the degree and stage of hepatic involvement Grey or yellow nodules may be seen on cross section scattered throughout the organ resembling miliary tuberculosis If the process is further advanced the organ may become granular or finely nodular showing increased resistance to cutting and thus resembling portal cirrhosis

Microscopically the sarcoid granuloma in the liver resembles the lesion seen in other organs Shay and associates on the basis of biopsy observations point out that the earliest lesion consists of an area of parenchymatous degeneration about 0 2 mm in diameter Exudative reaction absent at first appears later in the form of lymphocytic infiltration This area enlarges histiocytes epithelioid cells giant cells appear to form a tubercle The giant cells may contain an asteroid inclusion body The Schaumann inclusion bodies in giant cells consisting of dark staining laminated material are not very common in the hepatic lesion Longscope and Freiman emphasize the monotonous similarity of the sarcoid tubercle regardless of the organ in which it appears They also call attention to the relative sparsity of inflammatory cells around the aggregation of clear pale staining epithelioid cells This helps to distinguish the lesion from tuberculosis The central portion of these granulomatous lesions may undergo granular necrosis but this occurs only in scattered tubercles is confined to the center and is distinguishable from the caseation necrosis of tuberculosis by the presence of a delicate reticulum (Rakov and Taylor)

The sarcoid tubercles may be situated anywhere in the lobule but are most frequent in the portal areas Proliferation of fibrous tissue in the vicinity of the granulomatous lesions may result in complete distortion of the hepatic architecture and a peculiar type of cirrhosis Shay and coworkers found some of their biopsy specimens devoid of liver cells and completely replaced by fibrous tissue One patient reported by Longscope and Freiman developed ascites and a nodular cirrhosis

The spleen is involved with considerable frequency In the collected cases as well as those observed at the Massachusetts General and the Johns Hopkins Hospitals the incidence of splenic involvement was 63% The spleen may vary in size from slightly enlarged to enormous size weighing over 2000 gm The size of the spleen is not correlated with the degree of involvement since some of the small spleens were markedly involved The marked splenic enlargement is frequently due to portal hypertension and is associated with esophageal varices

Clinical Features

The age at which sarcoidosis is most commonly encountered is between 20 and 40 years There is no predilection for either sex Negroes are much more frequently affected than Caucasians and a ratio of 17 to 1 has been calculated (Ricker and Clark)

The liver is palpable in only a fraction of cases that show morphological involvement



Fig 90 Needle biopsy of liver (X 00) showing granuloma of Boeck s sarcoid The patient had no clinical signs of liver disease The liver was normal in size and the liver function tests were normal

This indicates that the liver can be the seat of sarcoidosis without clinical enlargement (Fig 90) The unobtrusiveness of the liver involvement is evidenced by reports of groups of cases of considerable size (8) without reference to liver enlargement or involvement (McCort et al 1947) Gendez and coworkers found palpable livers in only 3 or 13% of their 4 patients In their series of patients plus those they reviewed from the literature this organ was palpable in -3% of cases In 426 collected cases the liver was palpable in 74 or 17 3% (Table 72)

Splenic enlargement is detected clinically approximately as frequently as hepatic enlargement The spleen may be enormous in size When the spleen is markedly enlarged esophageal varices should be looked for Massive esophageal hemorrhage has been reported Marked enlargement of the spleen may also be associated with ascites and visible abdominal veins Spontaneous rupture of spleen in sarcoidosis has been reported (James and Wilson) The combination of splenic enlargement esophageal varices and dilated abdominal veins are indicative of portal hypertension which occasionally develops as a late sequela of this peculiar type of cirrhosis Splenic enlargement may exist for a long time before an accurate diagnosis is made The patient may be labeled as portal cirrhosis till a morphological diagnosis is made

Jaundice is another rare finding in sarcoidosis which may call attention to the liver Its presence along with hepato splenomegaly without other evidence of sarcoidosis may lead to a clinical diagnosis of cirrhosis as happened in the interesting case reported by Ross and Weinberg The jaundice is usually low grade may persist for years and be accompanied by pruritus A case similar to the above was reported by Dagradi and coworkers The jaundice in the Negro male was more intense Two patients in the Johns Hopkins series of 90 were jaundiced while Goeckerman found clinical jaundice in of 17 case When clinical jaundice is present hepato splenomegaly is almost invariably present and the patient is frequently febrile

While the mechanism of the production of

Table 72

Palpable Liver in Sarcoidosis

	Cases	Liver palpable	%
Ricker and Clark	195	17	8
Longcope and Freiman	14	35	4 6
Reisner	3	6	18
Harrell	11	6	54 5
Shay et al	1	7	33 3
Gendez et al	4		13 0
	4 6	74	17 3%

jaundice in this disease may vary as in many other conditions accompanied by icterus it seems unreasonable to attribute the jaundice to unrelated causes The finding of an elevated prompt reacting bilirubin a high alkaline phosphatase as well as bilirubinuria speak for regurgitation jaundice An extrahepatic obstruction can occasionally be responsible as was demonstrated in the markedly jaundiced patient studied by Shay and associates In this case a blood clot was found obstructing the cystic and common ducts Lymph node obstruction of the common duct has also been implicated The biliary obstruction is more commonly intrahepatic caused by parenchymal distortion and encroachment of the granulomas on the bile radicals

Liver Function Tests

Hyperbilirubinemia usually low grade is occasionally observed A serum bilirubin of 1 to 1 5 mg was observed by Shay and associates in 6 of their 24 patients Bilirubinuria and urobilinogenuria occur with the more marked hyperbilirubinemia

The bilirubin excretion test showed some retention of pigment in four patients in whom it was used (Harrell) This is additional evidence that the hyperbilirubinemia encountered is due to intrinsic hepatic involvement

Serum protein alterations have been observed long ago and are frequent but cannot be ascribed entirely to hepatic involvement The alterations have some resemblance to that found in hepatic disease but there are some differences as well Salvesen (1935) first pointed out that this disease is accompanied by increased serum protein at times to over 9 0 gm% and the elevation is largely due to an

elevated globulin While an elevated globulin is a feature of hepatic disease it also occurs in infections reticulo endothelial and mesenchymal disturbances The increase in serum globulin results in a reversal of the albumin globulin ratio Electrophoretic studies of the serum proteins in this disease showed marked elevations of the gamma globulin and some elevation of the beta globulin (Shay et al and Seibert et al) The alpha globulin fraction may decrease with the albumin It appears that the serum proteins return to normal when activity of the disease ceases If sufficient alteration of hepatic architecture takes place during healing the restitution of the serum proteins to normal may not take place

The determination of the gamma globulin is valuable since it may indicate activity of the disease as well as hepatic involvement This may be done by the simplified chemical or flocculation procedure (p 28)

The flocculation tests such as the thymol turbidity and cephalin cholesterol flocculation and colloidal gold are frequently positive This is to be expected from the alterations in the serum proteins These tests are usually only mildly abnormal The slight elevation of the thymol turbidity with a marked increase of the gamma globulin suggests that the gamma globulin elevation is not entirely the result of hepatic injury

Bromsulphalein retention is noted in a considerable number of patients with sarcoidosis further evidence that the hepatic dysfunction *is an important factor* in this disease

The serum alkaline phosphatase may become markedly elevated in the presence of jaundice Elevation of the enzyme has been found in non icteric patients and it could not be correlated with the *skeletal lesions Most patients with* alkaline phosphatase elevations show extensive hepatic involvement at autopsy, or biopsy However hepatic sarcoidosis has been demonstrated with a normal alkaline phosphatase

Alkaline phosphatase has been studied in liver tissue obtained from patients with hepatic *sarcoidosis* (Shay et al) Increased alkaline phosphatase was noted in the lymphocytes and in the vascular endothelium around the granulomas these two areas did not necessarily show simultaneous changes Decrease of hepatic cell phosphatase was noted in some It is interesting that elevated serum alkaline phosphatase was noted in all the four cases showing increase of the enzyme in the vascular endothelium

Needle liver biopsy has aided in the demonstration of the frequency of hepatic involvement with sarcoidosis The hepatic involvement was demonstrated in 75% of patients by Klatskin and Yesner and in 76 % by Shay and associates I have found the sarcoid granuloma in the liver in several patients with sarcoidosis and other investigators have had similar experience (Fig 90) The differentiation of sarcoidosis from other granulomas on the basis of the histologic picture may present difficulties no matter how the tissue is obtained therefore a specific diagnosis from a needle liver biopsy may be difficult or impossible One may have to be satisfied with a diagnosis of granuloma compatible with sarcoidosis and differentiate it from other granulomas with collateral data

Liver biopsy may be of great help in the diagnosis of sarcoidosis in cases in which easily accessible tissues such as peripheral lymph nodes or skin are not involved It is also of help in determining the precise nature of hepato splenomegalies of unknown etiology

Treatment

This should be directed against *the systemic* disease and in view of the frequency of hepatic involvement an effort should be made to protect this organ by dietary means This effort should be unrelenting in view of the likelihood of the development of cirrhosis with ascites and portal hypertension When these *complications occur they should* be treated like portal hypertension of other etiology (p 355) Splenectomy and spleno renal vein anastomosis has been successfully performed for this complication of sarcoidosis The recent suggestion that sarcoidosis may respond favorably to cortisone administration should evoke a note of caution lest one mistakenly treat tuberculosis which may show disastrous results from cortisone therapy

Non specific Hepatic Damage in Tuberculosis

The effect of tuberculosis on the liver is unique since it can damage the liver in three ways

1 involvement of the liver by the specific microorganisms (p - 2)
2 production of amyloidosis (p -25) and
3 non specific hepatic damag

The non specific injury of the liver is similar to the effect produced on this organ by other infections and consists of cloudy swelling fatty degeneration with the concomitant hepatic dysfunction

Fatty infiltration of the liver is a frequent concomitant of advanced tuberculosis It should be pointed out that in studying the response of the liver to the new antituberculous drugs the tendency to liver damage in this disease must be remembered Ullom in 1909 observed fatty infiltration of the liver in 35 of 100 patients In spite of the improvement of treatment of tuberculosis 30 years later Jones and Peck reported an autopsy incidence of 41 96% of fatty liver This may be explained on the basis of the identity or similarity of the lesions in fatal tuberculosis in the two periods Fatty liver is frequently seen in patients with tuberculous enteritis (Jones and Peck) which is accompanied by severe inanition and emaciation The fatty liver undoubtedly develops on the basis of starvation and has no specific relationship to the infection

The various therapeutic agents utilized in the treatment of tuberculosis may have a deleterious effect on the liver The new antituberculous drugs tibione (p 173) and isonicotinic acid hydrazide may have some hepatotoxic effect Tibione is the more hepatotoxic of the two Prolonged pneumoperitoneum produces no deleterious effect on the liver (Katzin 1952)

Hepatic dysfunction as measured by the usual liver function tests is noted in patients with tuberculosis in the absence of amyloidosis or direct involvement of the liver with the mycobacterium Bromsulphalein retention has been noted by using the older - mg test (Levinson and Siegel) as well as by the 5 mg test (Kruger and Gerber) More recently Hurst and coworkers performed a group of liver function tests in 18 patients with far advanced tuberculosis Bromsulphalein retention above 5% in 45 minute was found in four patients Two of these showed a dye retention of 18 and 20% the one with the greatest retention also had amyloidosis There were several patients with depressed hippuric acid synthesis a few with elevated alkaline phosphatase The total proteins were normal but several showed elevation of the gamma globulin Positive flocculation tests especially the thymol turbidity have been repeatedly observed in patients with pulmonary tuberculosis This may be due to the elevation of the gamma globulin which has been noted in patients with tuberculosis (Levin et al)

XII Diseases of Liver Associated with Inborn Errors of Metabolism

73 Hemochromatosis (Pigment Cirrhosis)

Hemochromatosis (also known as bronze diabetes pigment cirrhosis) is a disease caused by an inborn error in metabolism characterized clinically by skin pigmentation (bronzing) diabetes mellitus cirrhosis of the liver and sexual hypoplasia and pathologically by deposition of abnormal amounts of iron containing pigment (hemosiderin) and iron free pigment (hemofuscin) in various organs and tissues

Etiology

Incidence

This relatively rare disease was first described by Hartman and Chaussen in 1882 as bronze diabetes Von Recklinghausen seven years later pointed out that the pigments deposited in viscera and skin were hemosiderin and hemofuscin The rarity of the disease is attested by the fact that the total number of cases in the literature is about 500 Sheldon (1934) collected 311 cases Berk and Lieber added 125 cases making a total of 436 cases in 1941 *The more recently reported cases are few in number* and the reports deal with special features of the disease Its rarity is further attested by the observation of only 30 cases in over 15 years at the Mayo Clinic 17 cases in 26 years at Boston City Hospital 3 cases in 20 years at Jefferson Hospital in Philadelphia 3 cases among 160 000 admissions to Johns Hopkins Hospital and 4 cases among 5 000 autopsies at Bellevue Hospital At Michael Reese Hospital (Chicago) no patient with primary hemochromatosis came to autopsy in the past five years In 1951 two large groups of cases were reported totaling 53 patients (Althausen et al Marble and Bailey)

Sex

Hemochromatosis is predominantly a disease of males A 20 1 ratio of males to females was calculated by Sheldon but this observer thought the incidence in males might be even greater than that since many of the cases in females were poorly authenticated Of Butt and Wilder s 30 cases one was female This preponderance among males is related to the pathogenesis of the disease That it does occur in the female is unquestionable Three of 17 cases reported by Mills were in females and three of 23 cases reported by Althausen and associates were in females

Race

Little mention of the occurrence of the disease in Negroes is made in the American and in the European literature The Gillmans report numerous cases of hemochromatosis or rather cytosiderosis in malnourished African natives

but this entity differs in many respect from the idiopathic type One case in a Negro was recently reported by Krumm and Kahn

Age

In most patients the disease is diagnosed between the ages of 45 and 55 the youngest patient in whom the full blown disease was diagnosed was 20 years old However some of the symptoms may begin in childhood or adolescence in five of Sheldon's case the onset could be traced to the ages of 7 16 17 18 and 19 Butt and Wilder state that in one of their patients the disease probably began at the age of 10 they deduced this from the hepatic enlargement In another patient the onset of the disease according to their estimation was at the age of 17 Four of their patients were between 30 and 39 years of age Chesner reported a case (confirmed by autopsy) in a 14 year-old boy This patient had received blood transfusions so that one may suspect that the disease was exogenous hemosiderosis but this is refuted by the author because the iron content of the liver was more than 15 times that supplied by the transfusions

Familial Incidence

There is unquestionably a tendency for several members of one family to be afflicted with this disease The rarity of the disease makes the familial occurrences more significant Sheldon referred to five instances of the disease in brothers Lawrence reported hemochromatosis in brothers of three different families Among these were identical twins in whom the disease developed at the same time Rogers reported hemochromatosis in two brothers and a sister who had diabetes but no pigmentation In the sister a punch biopsy of the liver was negative for both cirrhosis and hemochromatosis There have been reports of other cases where siblings of patients with verified disease had diabetes or cirrhosis

In regard to hereditary transmission the evidence is not so convincing There is at least a suggestion but no positive proof that the parents of the patients in some of the reported cases had suffered from the same disease This familial tendency the occurrence in twins and possible hereditary tendency all support the hypothesis that the metabolic defect is congenital in origin

PATHOGENESIS

A search for a toxin as the agent responsible for hemochromatosis has been going on for several decades Alcohol has been incriminated by some as being etiologically related to this disease However the incidence of alcoholism in these patients does not support this contention Only about 25% of the patients consumed excessive amounts of alcohol

Mallory thought that contact with copper might be an important factor in the production of this disease This investigator produced pigmentation and cirrhosis of the liver in rabbits and sheep by administration of copper salts or metallic copper in powdered form He contended that industrial exposure to copper could be elicited in a significant number of these patient and that alcohol ingestion may produce a deleterious effect by its copper impurities The theory of copper intoxication is receiving little support In Korea where most of the cooking utensils are made of copper or its alloys the disease is very rare

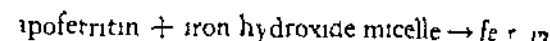
The theory of some specific toxin has received renewed support from the investigations of Herbut and associates This group reviewed 115 cases of hepatic cirrhosis that came to autopsy and found among them 12 case of diabetes mellitus In 51 of 60 cases in which histologic sections of the pancreas were available for study there was diffuse fibrosis Among this group were 6 cases with evidence of cirrhosis fibrosis of the pancreas and pigment deposition These investigators therefore theorized that there is a relationship among simple cirrhosis diabete and hemochromatosis They postulated a ureide as the toxic agent which produces cirrhosis and pancreatic injury the former aggravated by dietary deficiency the latter by the increased portal pressure Hemochromatosis follows because of abnormal iron retention from exogenous or endogenous sources To further substantiate this theory they showed that in one third of rabbits given injections of alloxan severe periportal necrosis of the liver developed Two animal developed diabetes and portal cirrhosis and showed minimal deposits of iron pigment in the liver

spleen and pancreas *They concluded there*fore that alloxan or some allied toxin may produce a chain of events culminating in hemochromatosis

The unique chemical disturbance in this disease *is the enormous quantity of iron found* stored in the tissues Thus *the iron in the* body may be 30 to 50 gm as against the normal of 4 5 to 5 gm and *normally* 2 5 gm of this iron is circulating in the blood stream The *iron stores in the normal adult male is* estimated at 1 2 gm to *1 5 gm (Haskins et al)* If the questions of how and why these enormous stores of iron accumulate were answered the riddle of hemochromatosis would be solved A *clearer insight* into this problem can be attained by a consideration of iron metabolism

Iron Metabolism

The body is unable to excrete iron except in minute amounts therefore it has to guard against excessive iron intake *There apparently* exists a mechanism that regulates iron absorption according to the need for this metal and the exhaustion of iron stores It has been shown by radioactive iron studies that a human being *whose iron reserves have been depleted by* hemorrhage may absorb 10 to 20 times the normal amount of iron and the chronically anemic dog absorbs 5 to 15 times the normal amount Sudden severe bleeding of a normal dog did not result in sudden increase of iron absorption but rather this occurred after a lapse of several days After iron administration resistance to absorption increased rapidly for several hours This suggests that a 'blocking agent appears in the duodenal and jejunal mucosa (sites of iron absorption) when iron is administered Indeed it has been shown that the duodenal and jejunal mucosa contains a protein molecule apoferritin (molecular weight *465 000)* and when iron is absorbed, it attaches *itself to apoferritin* to form ferritin



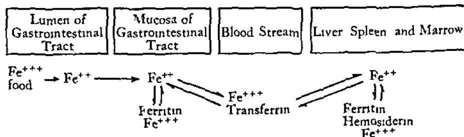
apoferritin + iron hydroxide micelle → *ferritin*

Ferritin increases rapidly in concentration in *duodenal and jejunal mucosa* when iron is being absorbed and apparently acts as the blocking agent While the ferritin concentration in the intestinal mucosa remains high iron absorption is blocked When sufficient iron *is picked up by the blood stream and carried* away to the depot the intestinal ferritin is reduced and further iron absorption can take *place*

The iron is transferred from the mucosa and is carried in the blood stream by a protein transferrin Normal *serum contains about 100* micrograms of iron per 100 cc bound to transferrin About two thirds of the transferrin is free of iron Transferrin carries iron to the storage depots or areas of utilization like hemoglobin carries oxygen Iron is stored in the liver the spleen and the bone marrow as the iron protein complex ferritin and hemosiderin It is probable that hemosiderin is an accumulation of ferritin in microscopic granules which are detectable by iron stain while the ferritin is so finely dispersed that it is not detectable by the usual histological techniques

An equilibrium normally exists among the ferritin stored in the tissues the iron bound transferrin of the blood and the ferritin in the intestinal mucosa When stored tissue iron is *depleted the tissues pick up iron* from the blood and the transferrin picks up iron from the ferritin of the intestinal mucosa the loss of the blocking agent (ferritin) results in increased absorption of iron

This may be represented diagrammatically as follows



(Modified from S Garnick Chem Rev *38* 379 1946)

Normally the total iron in the body remains constant. In hemolytic anemias there is an internal redistribution of iron with greater stores and less circulating iron. When excessive amounts of iron are administered parenterally in the form of iron compounds or blood transfusions the body stores of iron may be increased. This may also happen when some defect in the absorptive mechanism is present and excessive amounts of iron are absorbed from the gastrointestinal tract. The liver is the first organ that becomes filled with hemosiderin. When the liver becomes saturated the transferrin of the blood becomes saturated with iron and then it overflows into other organs. The increased iron, it is assumed, then damages the cells in which it is stored with fibrosis and dysfunction following.

Where does the excessive iron in hemochromatosis come from? The most obvious answer, and one advanced in the past, is that it comes from the iron of the erythrocyte. Against this is the absence of evidence of hemolysis and the rarity of severe anemia in this disease. The alternative source is increased absorption from the gastrointestinal tract. The evidence for this is as yet meager. According to the studies of radioactive iodine absorption by one group (Balfour et al 1942) no increased absorption was found in hemochromatosis. Fowler and Baker (1937) showed that in advanced hemochromatosis there was no increased absorption but in one case of early hemochromatosis markedly increased absorption was demonstrated. Dubach and co workers demonstrated increased retention of orally administered radioactive iron in one patient with hemochromatosis. Actually, since the defect is most likely congenital and the full blown disease does not become evident till the age of 50 only 1 gm of iron need be absorbed each year and only about 3 mg per day to yield a final 50 gm store. The rarity of the disease in females is explainable on the basis of loss of iron through menstruation, pregnancy and lactation. These physiologic functions may help to get rid of the increased iron absorbed and protect the female from this disease.

The next question in pathogenesis that needs to be cleared up is whether the hemosiderin indeed causes the tissue damage found in this disease. This is an attractive assumption but cannot be accepted as proved. In experimental animals injections of blood (Rous and Oliver 1918) and saccharated iron (Brown et al 1950) produced marked hemosiderosis but no cirrhosis was observed. In human transfusion hemosiderosis cirrhosis is rare; when it occurs other factors (such as anemia and toxins) may be responsible. So while the liver and pancreatic damage may be due to the irritating effect of the pigment, it is also possible that the congenital metabolic defect is responsible for the various pathologic changes in the involved organs as well as the abnormal iron absorption.

Transfusion Hemosiderosis (Hemochromatosis)

This entity of excessive stores of hemosiderin in patients who have received numerous transfusions is well recognized. Brown and co workers (1950) have added 10 cases of their own making a total of 40 cases in the literature. Other cases are reported by Frumin and co workers. This small number is deceptive since hemochromatosis and hemosiderosis due to hemolysis and transfusions is actually commoner than the idiopathic variety. At Michael Reese Hospital 3 cases of transfusion hemochromatosis came to autopsy in the past five years whereas no true case of idiopathic hemochromatosis was observed during this period. Whether the disease in any of these can be properly classified as hemochromatosis is doubted by Brown and co workers and Muirhead and associates. Their doubt is supported by the experimental and clinical observations mentioned above and also by the fact that the exogenous iron is deposited preferentially in other organs. The kidneys and the spleen are more heavily involved than in hemochromatosis. The cellular distribution within the organ may be different in the two conditions (see Pathology). The excessive deposits of iron is varified by chemical studies (Table 73).

Schwartz and Blumenthal (1948) however suggest that the differences are quantitative rather than qualitative between idiopathic hemochromatosis and the hemosiderosis due to blood transfusions, for which they propose the term exogenous hemochromatosis. They sug

TABLE 73

Iron Concentration Expressed as milligrams per Hundred Grams of Tissue

Specimen	Liver	Pancreas	Kidney	Lung
Normal Patients				
1	10 04	6 3	5 17	4 4
	4 08	4 44	10 00	17 75
3	21 41	6 4	11 03	11 77
4	16 2	10 13	10 28	16 19
5	1 36	8 84	14 0	19 3
6	10 93	9 05	1 4	7 65
7	21 01	4 75	4 43	8 77
8	8 68	9 46	11 16	13 9
9	17 44	7 39	11 05	14 9
10	14 86	7 14	11 13	14 6
Average	16 6	7 37	10 16	1 87
Cases of Transfusion Hemosiderosis				
1	967 46	105 38	94 48	81 94
2	869 68	—	77 46	71 51
3	573 33	678 0	45 85	74 96
4	162 86	—	16 91	39 05
5	41 93	62 9	35 9	15 99

E E Muirhead et al Arch Int Med 83 477 1949

gest that hemosiderosis exogenous hemochromatosis and idiopathic hemochromatosis are stages of one disease the chief differences being in the source of iron and the stage of the disease They explain the absence of the complete syndrome in the exogenous type by the shorter duration of the disease death occurring more rapidly from the primary disease Only 2 of their patients had diabetes and only 5 had skin pigmentation They postulate that if the process were to continue for a longer period of time more pigment would be deposited and more organs and systems would be involved

The severe anemia with concomitant anoxia undoubtedly complicates the picture in this syndrome The exogenous source of the iron and the accumulation in large amounts explain its development in younger persons and its greater frequency in females The iron deposition cannot in all cases be attributed to the iron content of the blood administered Thus Chesner s patient received 6 liters of blood which is equivalent to 2 75 gm of iron but the liver alone contained 47 gm of this metal Therefore other sources of iron must be looked for Hemolysis of some of the patient s blood

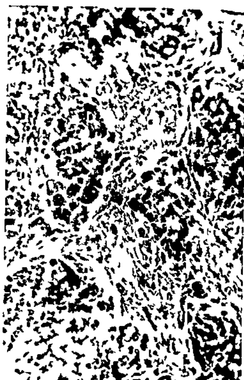


Fig 91 Pigment cirrhosis due to exogenous hemochromatosis Autopsy specimen Microscopic section (X 100) stained with Prussian blue to bring out the hemosiderin which is deposited in the parenchymal cells as well as in the fibrous tissue This 65 year-old man had had an aplastic anemia with an undetermined number of blood transfusions

in the hemolytic types of anemia and orally administered iron some of which may be absorbed are additional sources Increased intestinal absorption of iron in this type of hemochromatosis is suggested by Block and associates In the cases in which this discrepancy is very great some metabolic abnormality has to be involved to explain the excessive deposition of iron (Fig 91)

Another point of difference between this disease and idiopathic hemochromatosis is the relatively larger size of the spleen in the former In the cases reported by Wyatt and Goldenberg the spleens weighed 734 gm 1 015 gm and 2 105 gm ! The spleen in the last case was nearly as large as the liver While the liver was increased in size about 80% the spleen was increased 1 200%! The spleen in idiopathic hemochromatosis is only moderately enlarged

- to 3 times the normal size while the hepatic enlargement is more conspicuous

Nutritional Hemochromatosis (Cytosiderosis)

Another form of hemosiderosis of the liver is the type described by the Gillmans in malnourished South African natives The liver cells show iron containing and non iron containing pigments which result from deranged cellular metabolism secondary to the severe and prolonged malnutrition Since the pigments arise within the cells they refer to the hemosiderin as cytosiderin and to the hemofuscin as cytolipochrome They contend that these pigments arise from the cell mitochondria They describe a typical progression of hepatic changes which are divided into four types

Type 1 Varying amounts of fat are present in the liver

Type 2 Cytosiderin and cytolipochrome occur in hepatic and Kupffer cells only and in discrete granules

Type 3 This is similar to type except that iron containing pigment is aggregated into larger masses and in portal tracts as well as hepatic lobules

Type 4 This is the final stage which shows pigmentary cirrhosis of varying intensity

Type 1 was commonest in pellagrous infants Pigment cirrhosis was found in adolescents and young adults usually under 40 years of age This type of cirrhosis was found in 1 5% of all pellagrins but in the adult group the incidence was at times as high as 30%

The Gillmans propose the following concept for the pathogenesis of this type of hemochromatosis Malnutrition injures the liver cells The disturbed metabolism of these cells results in iron pigment deposition (cytosiderin) Iron is excreted from the liver through the bile into the gastrointestinal tract There it is absorbed by the duodenum and jejunum picked up by lymphocytes and carried in the lymphatics deposited in the regional lymph nodes and disseminated throughout the body

The relationship of diet to hemochromatosis is further emphasized by the following observations The iron intake in the Bantu was found to be quite high amounting to 100 mg to 150 mg per day (Walker and Arvidson) Pirani and his associates found hemosiderosis of the liver in cases of starvation from the Dachau concentration camp

Experimental Nutritional Siderosis

Taylor and co workers (1935) demonstrated that it is possible to produce hepatic siderosis in cats by pancreatectomy or ligation of pancreatic ducts and giving a diet rich in iron It was possible to produce the same phenomenon in the intact animal by a diet deficient in vitamin A It appears that vitamin A deficiency in these animals injures the intestinal epithelium and makes it more permeable to iron resulting in increased iron absorption Low dietary phosphates have been shown to increase iron absorption in the rat (Hegsted et al) These experiments offer more evidence that nutritional deficiency may result in abnormal iron metabolism and hemosiderosis

Summary

The views of pathogenesis may be summarized as follows In idiopathic hemochromatosis there appears to be an inborn error of metabolism resulting in increased iron absorption from the gastrointestinal tract and deposition in liver and other organs as hemosiderin As a result of and concomitant with this degeneration fibrosis and dysfunction of various organs ensues If excessive amounts of iron are introduced parenterally (blood transfusion etc) hemosiderosis of various organs also take place and clinical pictures similar but not identical with hemochromatosis are seen Finally malnutrition in human beings and animals (cats) may result in deranged iron metabolism and hepatic hemosiderosis and pigment cirrhosis The relationship of nutritional deficiency to idiopathic hemochromatosis is uncertain but deserves further exploration

Etiology and Pathogenesis—Summary

Idiopathic Hemochromatosis

Age 45-55

Sex Males Females 20 1

Familial Tendency

Inborn metabolic defect → increased iron absorption from

Gastrointestinal tract deposited as

hemosiderin in liver pancreas, skin and other organs

Exogenous Hemochromatosis

- Age any
- Sex Males and females equal
- Numerous blood transfusions
- Iron deposited as hemosiderin in liver pancreas etc, with disturbance of function Spleen and kidney show heavier deposits than above

Nutritional Hemochromatosis

- Age Under 40
- Sex No difference between sexes
- Race African natives, also demonstrated in Caucasians
- *Nutritional deficiency produces abnormal iron metabolism in liver cell eventual increased intestinal absorption*
- Vitamin A deficiency in cats produces increased intestinal absorption of iron
- Dietary phosphate deficiency produces increased intestinal absorption of Fe in the rat

Pathology

The outstanding pathologic feature in this disease is the accumulation of pigments in various organs and tissues The three pigments in the order of their importance are (1) hemosiderin ( ) hemofuscin and (3) melanin

1 Hemosiderin contains about 55% iron Its reactions are not typical for ferric iron and it does not give any reactions for ferrous iron The iron is combined with a protein as noted above It is deep *yellow and it may be dispersed in fine granules or* in large masses that are visible to the naked eye Histologically it is most easily identified by staining blue with potassium ferrocyanide Its distribution in the body is widespread with a special affinity for glandular organs The greatest amount is found in the liver and *the pancreas but every secretory gland* in the body may contain some even the male breast

Table 74

W ght / L	N mb / C
Below 1 500 Grams	10
1 500– 000 Grams	21
2 000–2 500 Grams	
2 500–3 000 Grams	4
3 000–3 500 Grams	16
Above 3 500 Grams	9

J H Sheldon Oxford Uni Press 1935

The epithelium of the excretory ducts may contain hemosiderin in small amounts but it is mainly found in smaller ducts Endocrine glands are extensively affected—parathyroids thyroid adrenals and anterior pituitary The posterior lobe of the pituitary is usually free from pigment and in the adrenals the deposit is chiefly in the zona glomerulosa The islets of the pancreas are involved in 4 out of 5 cases The kidneys and the germinal epithelium of the testis are uninvolved or only slightly involved The capillary endothelium of the testis contains large amounts The escape of the kidney from hemosiderin deposit *is in contrast to the findings in hemosiderosis* due to hemolysis or blood transfusions in which renal involvement is marked

Striated muscle is involved but smooth muscle almost never contains hemosiderin The heart muscle contains this pigment in 90% of cases often in *large amounts*

The reticuloendothelial system including Kupffer cells of the liver spleen and bone marrow contains large deposits The spleen and bone marrow are relatively less involved in this disease than in hemosiderosis due to blood destruction The pigment is also found in lungs cartilage of joints and respiratory tract as well as in connective tissue which is involved to the greatest extent in the organs of greatest predilection the liver and the pancreas

Hemofuscin is the iron free pigment which contains 3 7% sulfur It is very dark in color almost black and is probably related to the melanins It stains bright red with basic fuscin It is widely distributed but not in the same tissues as hemosiderin It is found to some extent in the glandular organs but with more frequency in connective tissue Smooth muscle is however a site of predilection as far as concentration and frequency of occurrence are concerned The smooth muscle of the genital and alimentary tracts may be loaded with hemofuscin to the point of imparting the gross brown color to these structures The longitudinal muscles are more heavily involved than the circular The smooth muscles of the arteries also contain heavy deposits of this pigment

3 Melanin is deposited in excessive amounts in the skin and contributes to the peculiar color This pigment is also responsible for the occasional pigmentation of the mucous membranes of the patients

The liver has a peculiar rusty or reddish brown hue which is due to heavy pigment deposits This organ is usually enlarged weighing between 000 and 3 000 gm (Table 74) However in 10% of cases it is smaller than normal Sheldon refers to a liver weighing as little as 1 100 gm and to one weighing as much as 4 1 0 gm The organ is firm and hard in consistency and cuts with difficulty The surface is finely nodular or hobnail similar to that in alcoholic cirrhosis Occasionally prominent areas of regeneration are separated by deep scars On section the pseudolobulation stands out The

usty colored pigment areas are interlaced with the ess pigmented scar tissue and are studded with un igmented regenerating nodules Occasionally the car tissue is as heavily pigmented as the paren hyma and the sections present a uniform color

Microscopically the picture is that of portal cir hosis the term hypertrophic cirrhosis is unjustified or this reason and because hypertrophic cirrhosis is usually accompanied by marked icterus which is not the case here The architecture shows a loss of he normal relationship of the central vein to the ver lobules Thick strands of fibrous tissue are seen dividing the pseudolobules (Figs 91 and 92) Much pigment is found in the liver cells and especially in he periphery of the lobule Rarely the center of the obule is entirely free of pigment The reverse of this obular distribution of pigment has been reported The pigment first appears in the center of the cell but the entire cell eventually becomes filled The gradations are from fine dust like particles to large granules filling the cell The Kupffer cells are usually heavily laden with pigment The heaviest concen tration in these cells is in the region of the greatest parenchymal cell pigmentation The parenchymal cells are the first ones to become pigmented with the Kupffer cells picking up the pigment from over burdened hexagonal cells The reverse is true in hemosiderosis due to iron injections or blood trans fusions in which the Kupffer cells pick up the iron first and are usually more heavily involved than the parenchymal cells

Evidence of degeneration as well as regeneration of liver cells is seen The regenerating liver cells may contain little or no pigment The fibrous tissue con tains variable amounts of pigment frequently as much as the parenchymal cells but may contain more and less The pigment is both intracellular and extracellular The bile ducts contain a small amount of hemosiderin The vascular endothelium contains the iron pigment while hemofuscin is found in abundance in the media of arteries and veins The iron free pigment is found only rarely in the par enchymal cells

The pancreas varies in size but is usually larger than normal Its deep brown color bespeaks its heavy hemosiderin content The pigment is deposited in the acini as well as in the islet cells Marked in crease of fibrous tissue both intralobular and inter

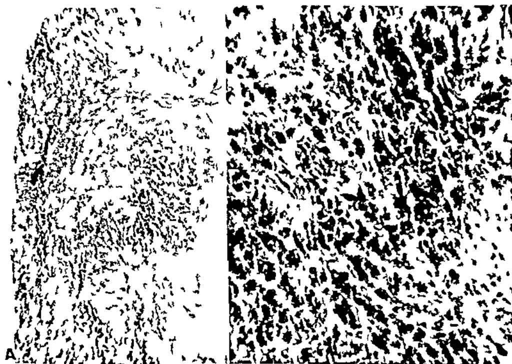


Fig 9 Needle b ps of l p tient with h mochromato The needle b p s prov d the d gnos (pag 547 case 1)

A Sect s (X 70) are sta d w th l n bl e and co ter sta d with b c f ch The re d to t f rch t ct r fib d m ked h mos der

B Sh w (X 80) th t the hem sid r n (bl k in ph t graph) is w th n th hepat c cell Th iron p gment was l d p it d the fibro t

lobular occurs in 90% of cases. In addition to pigmentation the islets of Langerhans are involved by fibrosis and are reduced in number.

The spleen grossly is not markedly discolored. It is enlarged in size but not markedly. Usually it is [illegible] to 3 times the normal size. Considerable variation in size is reported, however, with weights between 114 and 950 gm. It may be softer or firmer than normal. Hemosiderin pigmentation is present but is much less pronounced than in the liver. Hemofuscin deposits are found chiefly in the vessel walls.

The kidneys are normal in size and color. Pigment deposition is slight or absent in true hemochromatosis. In hemosiderosis this organ is heavily involved. *Hemosiderin, when present, involves chiefly the* convoluted lobules and the loops of Henle. The glomeruli are less frequently affected. Hemofuscin may be found in about half the cases, chiefly in vessel walls.

The gastrointestinal tract is noteworthy chiefly because of the heavy deposit of hemofuscin in the smooth muscles of the small intestine, which may impart to it a brown color. One feature of interest is the finding of shortening of the small intestine in some cases of this disease. Hemosiderin deposits are found in the glands and mucosa of the stomach as well as the intestine. The esophagus is apparently infrequently involved.

Heart muscle shows deposition of hemosiderin in all cases, and the pigmentation may reach an extreme degree. Occasionally the muscle fiber is replaced by *a mass of pigment. In spite of this fibrous tissue is* usually not excessive. Degenerative changes of muscle fibers are also reported.

The endocrine glands, including the parathyroids, the thyroid, the adrenals and the pituitary, are heavily pigmented. The parathyroids are next to the liver and pancreas in the amount of hemosiderin deposited. *In spite of the heavy pigmentation of the* parenchymal cells there is no increase in fibrous tissue. The thyroid, on the other hand, contains only moderate amounts of pigment in the glandular cells but shows markedly increased fibrosis. This lack of correlation between amount of hemosiderin and fibrosis conflicts with the theory that there is a cause and effect *relationship between the two.*

The adrenal gland shows a selective deposition of hemosiderin in the zona glomerulosa. This area is involved in all cases in which pigment deposition is found in this gland. The zona fasciculata is affected to a much lesser degree and less frequently than the above area, and the zona reticularis least of all. The medulla shows *some hemosiderin deposit.* Fibrous tissue is not generally increased in this organ. Sheldon reported no case of complete destruction of these glands in hemochromatosis, but this complication has been reported.

The pituitary gland shows a brown pigmentation to the naked eye. The hemosiderin deposits are chiefly in the anterior lobe. *The pars nervosa may be* free of pigment. Sheldon *refers to cases in which* the hemosiderin deposits were confined chiefly to the basophil cells, which were heavily loaded, while the eosinophil cells were almost free of pigment. Hemofuscin is seen in the musculature of the vessels of this gland. No mention is made of increased fibrous tissue.

The testis is usually grossly normal but may be smaller and softer than normal. Microscopically atrophy of the germinal epithelium is the most common change. The amount of pigmentation in this organ is not great, and increased connective tissue is rare. Hemosiderin is found in connective tissue and with great constancy in blood vessels. Hemofuscin rarely occurs in the blood vessels of the testis but frequently occurs in connective tissue. This lack of localization in the blood vessels is unique for this organ.

The skin shows increased melanin deposits in the deeper layers of the epidermis. Hemosiderin deposits are heavy in the sweat glands but may also occur in large amounts in connective tissue. The endothelium of the capillaries and smaller vessels contains iron pigment, but the sebaceous glands are *free from it. Hemofuscin is found in the* walls of the blood vessels.

The central nervous system is almost entirely free of pigment deposits. The choroid plexus contains a good deal of hemosiderin. The lymph nodes show varying amounts of pigment depending on the region they drain. The portal and pancreatic lymph *nodes are most heavily involved.*

Metal and mineral content of tissues varies from normal in respects other than iron. The iron content of all the tissue may be 10 to [illegible]0 times the normal values, and in the liver this is increased 40 times. The average content of iron in a group of cases is reported by Sheldon as 1 36 gm. The copper content of tissues is also increased. *The liver contains* about 4 times as much copper as the normal liver. The pancreas and thyroid contain abnormal amounts of copper. There is some evidence that the zinc and sulfur contents of tissue are likewise elevated. The calcium content of tissue is also slightly increased and in some respects parallels the iron deposition. *Even though the blood calcium is not abnormal* the increased calcium content of tissue is of interest because of the intense pigmentation of the parathyroid glands. Some osteoporosis has been noted and calcifications in the spleen and lymph nodes have been reported.

Pathology—Summary

Pigment deposits

Hemosiderin

All glands: liver, pancreas, gastric and intestinal glands, parathyroids, adrenals, etc., sweat glands

Striated muscles including heart muscle

Hemofuscin

Smooth muscles of

Gastrointestinal tract

Blood vessels

Melanin

Increased in deeper layers of epidermis

Fibrosis

Portal cirrhosis of the liver

Fibrosis of the pancreas

Clinical Features

1 Pigmentation of the skin is the most striking symptom and finding In the cases reviewed by Sheldon it was the first symptom in over one quarter of the cases (25 7%) In the Mayo Clinic series it was the first symptom in 40% of the cases While pigmentation of the epidermis is of sufficient importance to be incorporated in the nomenclature (bronze diabetes) it is not universally present It was present in 83 8% of Sheldon s cases and in all but one case in the Mayo Clinic series and Althausen s series John and Chesner reported one case each without skin pigmentation A Negro patient with hemochromatosis showed an absence of hemosiderin in the skin So while pigmentation is almost always present it may be absent in true hemochromatosis

The color of the skin pigmentation has been described as brownish gray slate gray slate blue bronze or grayish brown It has been referred to as a color intermediate between the typical melanosis of Addison s disease and the slate gray of argyria Hemosiderin deposit is one of the diagnostic features of this disease and is responsible for the peculiar color of the skin of these patients However melanin is also present in increased amounts in some and may be the only pigment The relative amount of these two pigment results in the variations of color in patients with this disease

Hemofuscin is not important so far as skin pigmentation is concerned

The pigmentation is distributed throughout the skin but exposed areas may be more deeply pigmented This may be due to the increased melanin in the e areas Localized areas of pigmentation of the skin as well as of mucous membrane have been attributed to melanin

The mucous membrane pigmentation is brown in color and has been described involving the gingiva and the hard and soft palate In the 57 cases analyzed by Hellier the incidence of the two pigments in the skin was as follows

	Present	Absent	Not mentioned
Hemosiderin	48	5	4
Melanin	35	1	10

The increase of skin melanin and the heavy deposit of hemosiderin in the zona glomerulosa of the adrenal cortex has evoked the question of a cause and effect relationship All of Hellier s patients who showed melanin pigmentation also showed hemosiderin deposits in the zona glomerulosa It is tempting to assume that damage to the adrenal gland is responsible for the increased pigmentation Rogers has attempted to clarify this point by determining the amount of cortin excreted by a patient who showed both of the above features The values found in this patient were not below normal The method he used determined chiefly the gluco corticoids excreted The mineral corticoids however are not related to pigmentation and an assumed decrease of these could not pos ibly explain the increased pigmentation A lack of androgenic hormones would produce an opposite effect Therefore there is a lack of good evidence that the increased melanin pigment is due to the involvement of the zona glomerulosa but it may be due to local factors in the skin

The chemical similarity between hemofuscin and melanin suggests that the increased melanin may be related to the widespread metabolic disturbance that occurs in this disease The histological chemical and spectroscopic methods of detecting iron pigment in the skin will be discussed below

2 Cirrhosis of the liver is another of the diagnostic features of this syndrome The patient may consult a physician because of symptoms referable to the liver The presenting symptoms may be dyspepsia epigastric pain jaundice abdominal enlargement dyspnea or edema Liver enlargement is noted in 90% of

cases The enlargement of this organ is considerable the lower edge frequently reaching the umbilicus The liver is firm and smooth and tenderness is either absent or very mild Enlargement of the spleen is neither as common nor as marked as that of the liver A palpable spleen has been described in 30% to 60% of cases

Jaundice is not common in this type of liver disease when it is present it is usually mild but contributes to the bizarre discoloration of the skin In the Mayo group of 30 cases with early diagnosis no icterus was noted However jaundice was noted in 9 of 17 cases from Boston City Hospital (Mills)

Ascites is a late manifestation in this disease and is of even more serious prognostic omen than in other types of cirrhosis In the absence of complications the fluid is clear amber True caput medusae or prominent abdominal veins may be present Esophageal varices due to increased portal pressure with erosion and hemorrhage from these have been described Spider nevi are less common then in nutritional cirrhosis Liver function tests (to be discussed below) are only mildly deviated from the normal

3 Diabetes mellitus is another diagnostic feature which has been imprinted on the nomenclature The initial symptoms may be referable to this phase of the disease in 25% of cases Diabetes is eventually found in 70% to 86% of cases *The diabetes is usually mild* and for this reason may not be detectable by urinary studies An elevated fasting blood sugar level may be the only evidence of this abnormality If glucose tolerance tests were done in all suspected cases of this disease diabetes would be discovered in a higher percentage of cases than stated above This fact is demonstrated by the case described below (p 547)

The mildness of the diabetes permits easy control with diet or small doses of insulin Acidosis is uncommon until late in the disease when insulin resistance may make treatment difficult and ketosis frequent The diabetes may be of moderate severity (Marble and Bailey)

4 Sexual hypoplasia is the last of the diagnostic features of this disease It is less common than the previously mentioned features and is said to occur in about 20% of cases This however may depend on the stage of the disease *being more frequent in the more advanced* cases

The symptoms and findings in this group consist of impotence lack of ejaculation scanty axillary and body hair and female pubic escutcheon There may also be a decrease of facial hair with slower growth necessitating less frequent shaving and decreased size of the testes

The sexual hypoplasia is probably secondary to the involvement of the endocrine glands with heavy deposits of hemosiderin The pituitary gland is most likely responsible for this The testicular atrophy is also secondary to the pituitary involvement since the gonads are not heavily pigmented In the presence of advanced liver dysfunction the feminizing feature may depend on excessive accumulation of estrogens due to the inability of the liver to inactivate these hormones (Chapter 63)

Maddox described retinal changes which he called diagnostic of this disease He observed discoloration of the retina in three patients This consisted of an ochre colored background in the periphery of the fundus

Other clinical findings while they may not be of diagnostic importance or may even complicate the diagnostic problem may add to the intriguing features of the disease The *blood pressure is frequently low* but may be normal or even slightly elevated Hypotension along with excessive pigmentation with melanin brings up the question of *adrenal insufficiency* Many of the other features of the disease such as low glucose tolerance edema and salt retention are all contrary to the findings in Addison s disease A complete picture of adrenal cortical failure in hemochromatosis is rare but several such instances are found in the literature Hurxthal reported a case of a 57 year-old physician in whom the disease was diagnosed on the basis of a positive skin biopsy and who suffered adrenal failure on sodium restriction However this patient had severe anemia which is also rare in this disease Simpson in a review of cases of combined Addison s disease and diabetes mellitus found

two cases of hemochromatosis One of these patients had fibrosis and the other tuberculosis of the adrenal gland If adrenal insufficiency supervenes the pre existent diabetes becomes ameliorated

The hypotension can be explained on a basis other than adrenal insufficiency In many debilitating chronic diseases especially when malnutrition plays a role hypotension is seen It is intriguing to speculate that in this type of liver disease the vasodepressor material (VDM) of Shorr may be a potent factor in producing the lowered blood pressure It is postulated that VDM may be identical with ferritin and if hemosiderin is a form of ferritin we have a disease with a tremendous amount of VDM If this theory is correct one may well wonder why the blood pressure is not universally depressed in this disease unless one assumes that a vasoconstrictor factor in some of these patients compensates for the VDM

Direct effect on the vascular system may also be involved in the pathogenesis of the hypotension The large deposits of hemofuscin in the musculature of the blood vessels may have some effect on vascular dynamics

The changes in the heart muscle may have a similar effect Indeed cardiac involvement has been neglected in the clinical discussion of this disease a pointed out by Petit The French literature contains many references to cardiac involvement The dyspnea which has been mentioned under cirrhosis may be due to cardiac involvement Edema cough orthopnea and pulmonary congestion may be due to cardiac factors Horns and Blumer and Nesbit reported cases of hemochromatosis in which the patient died in congestive heart failure Blumer and Nesbit s patient showed extensive myocardial fibrosis Petit reported a case of complete heart block Other cases of auriculoventricular block as well as auricular flutter and auricular tachycardia have been reported In the French literature there are a number of cases of young adults with bronze diabetes in whom heart failure developed Myocardial infarction in hemochromatosis has been reported (Doane et al) Cardiac complications may be seen more frequently in the future with improved therapy of diabetes and cirrhosis

Gastrointestinal symptoms have been mentioned under symptoms referable to the liver However diarrhea constipation vomiting and generalized abdominal pains may be dependent on changes in the hollow abdominal viscera The extensive deposition of hemofuscin in the mu culature of the intestine and the hemosiderin pigmentation of the intestinal glands may be responsible for these symptoms

Apathy and drowsiness are occasionally noted and may depend on endocrine and metabolic factors since the nervous system remains undamaged except in rare instances (page 550)

Laboratory Findings

The blood count is usually around the lower limits of normal The erythrocytes are over 4 0 million and hemoglobin is about 80% However cases with mild anemia in the vicinity of 3 5 million red cells have been reported In the terminal phase of the disease anemia may become more marked If bleeding from esophageal varices develops the anemia may be profound The leukocytes and thrombocytes are within normal limits

A diagnostic feature in the blood is the increase of the serum iron and the saturation of the iron binding protein Normally only one third of the transferrin has iron attached to it (approximately 100 micrograms per 100 cc) In advanced hemochromatosis nearly all the transferrin is bound to iron The average saturation of the serum iron binding protein was 94% in patients with hemochromatosis as compared with 41% in normals (Gitlow and Beyers)

The basal metabolic rates were usually found to be elevated in the cases reviewed by Sheldon in all but four the rates were in the positive range This is surprising in view of the heavy hemosiderin deposit in the thyroid gland This again confirms the suspicion that the iron is not as toxic to cells or at least certain cell as is assumed by some workers

X ray may show increased density of the liver shadow because of iron depo it

The liver function tests do not show marked

abnormality until late in the disease, when all laboratory findings of cholemia may be present. The serum bilirubin is normal or slightly elevated in some cases. The sulfobromophthalein (bromsulfalein) sodium test may show mild to moderate retention. The flocculation tests may be slightly positive. The plasma proteins and especially the albumin may be depressed. This may be especially true in the presence of ascites. The alkaline phosphatase may be elevated. Cantarow and Bucher described a case with hypercholesteremia and xanthomatosis, which is a rarity.

Glycosuria and/or hyperglycemia may be present; even if these tests are normal, a glucose tolerance test may show a marked and persistent elevation of the blood sugar.

The diagnostic laboratory procedures consist of finding hemosiderin in various tissues and fluids. Its detection in the skin, liver, urine and ascitic fluid is a crucial factor in diagnosis. Hemosiderin may be detected in the skin by (1) histological, (2) chemical or (3) spectroscopic methods. The latter two methods depend upon the demonstration of excessive amounts of iron.

1. By means of a skin biopsy and appropriate staining with potassium ferrocyanide, the iron-containing pigment can be seen in the propria of the sweat glands and around the capillaries of the upper part of the cutis; this is nearly diagnostic. The skin used for this purpose should be obtained from the upper part of the body. The lower extremities, subject to trauma and stasis, may normally contain increased amounts of hemosiderin.

2. Fishback described an in situ chemical test for detecting increased iron in the skin. The test is performed by the intradermal injection of 0.1 cc. of equal parts of 0.5% potassium ferrocyanide and 0.01 N hydrochloric acid mixed beforehand. A bluish color may appear immediately at the site of the wheal; this darkens to a deep blue within five minutes. This test is simple and is not painful; it can quickly differentiate the skin pigmentation of Addison's disease, argyria and hemochromatosis. Only in hemochromatosis is a positive reaction obtained.

3. Iron content of the skin has been determined spectroscopically by Magnuson and Raulston, who found these values 5 to 10 times that of normal skin. The iron content of normal skin has been found to be around 1 mg. per 100 gm. of tissue. These workers found the iron content of three patients suspected of having hemochromatosis (later proved) to be 9.8, 9.8 and 9.9 mg. per 100 gm. of tissue. Two of these were confirmed by histological staining procedures; the third showed no iron pigment histologically. This is interpreted by the authors as a very fine dispersion of the iron pigment, so that it remained undetected by staining procedures.

Urinary siderosis or excretion of hemosiderin-laden tubular epithelium or free clumps of this material can be detected according to the method of Rous. A fresh specimen of urine is centrifuged and to the sediment is added 5 cc. each of 2% potassium ferrocyanide and 1% hydrochloric acid. This is again centrifuged in 10 minutes and the sediment is examined microscopically under a cover glass after the addition of hydrochloric acid solution. Intracellular or extracellular hemosiderin turns blue. Ammonium sulfide can be used instead of the acid ferrocyanide mixture; with this reagent the pigment turns black. This test is positive in hemochromatosis or any other type of renal siderosis which may occur in pernicious anemia or hemolytic anemia.

Hemosiderin in macrophages of ascitic fluid has been detected by Humphrey and co-workers. The macrophages contained golden brown pigment which gave a positive reaction with ferrocyanide.

Detection of pigment (hemosiderin and hemofuscin) in the liver by needle biopsy is probably the most diagnostic of all procedures. The technique of needle biopsy is described in the appropriate chapter. We diagnosed hemochromatosis by this means (see below) in our case, and this has also been reported in the literature.

Topp and Lindert reported six cases of hemochromatosis diagnosed by needle liver biopsy. The skin in these cases was not pigmented, and neither the intradermal test nor biopsy of the skin in the cases in which they were used revealed iron-containing pigment. All the tests described above depend on the involvement of the particular organ or tissue

with pigment deposition Since the liver is universally involved while the skin may be spared in as high as 15% to 20% of cases and the kidney more frequently the liver is the most likely organ to yield a positive diagnosis Althausen and co workers made the diagnosis in some of their patients by gastric biopsy

Diagnosis

The diagnosis is easy when the disease is kept in mind and the four diagnostic features skin pigmentation diabetes cirrhosis and sexual hypoplasia—are present However as has been pointed out above *one* or more of these features may be absent and the others may have to be looked for The diabetes may not become apparent unless glucose tolerance tests are done The nature of the skin pigment may have to be determined by the chemical or histological tests described above Hemosiderin should be looked for in the other body fluids and finally liver biopsy may determine the diagnosis when other methods have failed If hemochromatosis were considered in all cases of cirrhosis and diabetes more instances of the disease would be found

When skin pigmentation is present the disease may be confused with melanosis argyria and Addison s disease In these the color of the skin is different and the identity of the pigment can be detected by microscopic examination of the skin or other tests described above When the skin in hemochromatosis contains only melanin other evidence has to be secured In Addison s disease the glucose tolerance would be even better than normal edema is always absent and sodium loss not retention would be present A large liver and spleen would help to dispel the confusion and liver function tests and finally liver biopsy would clinch the diagnosis

In the differential diagnosis therefore the following diseases should be considered (1) portal cirrhosis ( ) diabetes mellitus (3) Addison s disease (4) argyria and (5) melanosis

The following case illustrates the diagnostic problem

Case 1

A 7 year old man had sought medical care five years before (1945) he was seen by us because of upper abdominal pain dyspnea and ankle edema Shortly thereafter he was found to have a large liver and a diagnosis of cirrhosis was made He was seen off and on at the clinic where he was subsequently treated for hemorrhoids On admission to the hospital in 1950 his chief complaints were weakness fatigability anorexia upper abdominal discomfort and loss of weight

It was noted that his skin was dry scaly and dark brown in color There were localized areas of increased pigmentation over the abdomen and chest Mucous membranes were not pigmented Spider nevi were noted over the upper part of the chest and the neck Palmar erythema was present The hair on the chest and in the axillas was scant His blood pressure was 156 79 and the pulse rate 84 The liver was palpated four fingerbreadths below the costal margin and was very firm and slightly irregular but not nodular The spleen was not palpable Slight pretibial edema was present

Laboratory findings The urine showed no glucose The red blood cell count was 4 100 000 the hemoglobin 13 7 gm and the white blood cell count 7 800 Serum chlorides sodium and glucose were normal

Glucose tolerance

Fasting blood sugar 108 mg per 100 cc of blood

1 hr 205 mg
hr 166 mg
3 hr 1 5 mg

The electrocardiogram was normal

Liver function test

Serum bilirubin 0 7 mg
Cholesterol 16 mg %
Esters 67 5 mg %
Cephalin cholesterol flocculation 3+
Sulfobromophthalein retention 18% in 45 min
Total protein 6 6 gm
Albumin 5 gm
Globulin 3 8 gm
Alkaline phosphatase 5 Bodansky units

Tests for hemosiderin

Intradermal skin test negative
Urinary sediment —negative
Skin biopsy —negative
Liver biopsy —positive for iron pigment and cirrhosis

Diagnosis Pigment cirrhosis (hemochromatosis) (Fig 92)

This case reveals the difficulty of making a diagnosis both from the clinical and from the laboratory point of view when the picture is incomplete The patient was followed for a number of years with a diagnosis of portal cirrhosis later a diagnosis of Addison s disease was entertained On his final admission the clinical impression was hemochromatosis although there was no evidence of diabetes The glucose tolerance was however of the diabetic type The increased skin pigmentation was due to melanin and not hemosiderin The diagnosis was established by the liver biopsy

Clinical Features and Diagnosis—Summary

Bronzing of skin
Ochre pigmentation of fundus
Large, firm liver
  Tests indicative of cirrhosis
Diabetes
  Abnormal glucose tolerance
  Glycosuria
Sexual hypoplasia
Hemosiderin in skin
  Intradermal test
  Biopsy
Hemosiderin in Liver
  Biopsy
Hemosiderin in urine or ascitic fluid
Increased serum iron and saturation of iron binding protein

Treatment

The therapeutic approach in this disease is directed toward the basic metabolic disturbance and toward disturbance of the major organs involved Elimination of the dysfunction of these organs is accomplished by treatment of the diabetes and cirrhosis Early the diabetes is mild and may be treated with diet alone or small doses of insulin Diabetic acidosis is no longer common and except in the late stages responds readily to insulin On the other hand insulin hypersensitivity may also occur It should be remembered that the diet should contain an abundance of carbohydrates and protein since we have to treat the damaged liver along with the diabetes

If the cirrhosis is the dominant feature of the disease therapy should be directed mainly toward it Portal hypertension and hemorrhage from esophageal varices should be treated by the same measures as described in Chapter 50

The skin pigmentation has been reported to regress as a result of vigorous treatment of the diabetes This apparent decrease of pigmentation may be due to changes in the translucency of the superficial layers of the skin with decreased visibility of the pigment deposited Cantarow and Bucher have reported the use of large doses of ascorbic acid to decrease melanin deposits in the skin This effect may be related to the role of vitamin C in melanin metabolism

Treatment directed toward decreasing iron absorption and ridding the body of the excessive iron stores in the most logical approach Decreasing iron intake by reducing the iron in the food is impracticable Diets high in phosphates may reduce iron absorption by the formation of insoluble iron phosphates The use of repeated phlebotomies to mobilize the excessive iron deposits for erythropoiesis has been reported by Davis and Arrowsmith This seems to be a promising approach It offers evidence that the iron of hemosiderin can be utilized The phlebotomies should be done cautiously especially in severe liver disease and would have to be carried out over a long period of time It would be important to make the diagnosis early so that this treatment can be started before the iron deposits have become enormous

Prognosis and Complications

All the evidence points to the fact that this disease is very insidious and exists for many years and decades before the diagnosis is made When the disease is well established much tissue damage has taken place and the course may be a fairly rapid downhill one Hence Sheldon gave a prognosis of about 18 months after diagnosis was established Diabetic acidosis was the cause of death in 50% of his group of 119 cases in which the cause of death was known With the modern treatment of diabetes with insulin this major cause of death should be and has been markedly reduced Among Butt and Wilder s cases one patient survived

for 13 years two for 9 years and one each for 8 and 7 years Recent studies likewise indicate a better prognosis

The next commonest cause of death is cirrhosis Thirteen patients (11%) died of cirrhosis six from hematemesis and seven from hepatic failure Ascites is a poor prognostic sign Pneumonia and tuberculosis are next in frequency as a cause of death Our present approach to the therapy of all these conditions holds out the hope of increased longevity

Primary carcinoma of the liver is the most serious complication of hemochromatosis Up to 1945 Oshlag and co workers collected 37 cases of this complication or five more cases since 1941 According to Berk and Lieber s statistics this complication occurs in about 7% of cases and has been invariably fatal Warren and Drake found 6 primary carcinomas of the liver in o autopsies on patients with hemochromatosis However even in this almost hopeless complication an attempt at surgical removal of the tumor may be made This complication may be suspected from a sudden increase of size or nodularity of the liver fever leukocytosis and hemorrhagic ascites Since the neoplastic cells do not store iron pigment an x ray of the liver may reveal a relatively radiolucent area at the site of the tumor This complication may be discovered earlier by successful needle biopsy of the liver

Treatment—Summary

Diet high in protein carbohydrates and phosphates
Insulin
Phlebotomies

74 *Hepatolenticular Degeneration (Wilson's Disease)*

Introduction

The rare and curious disease which shows degenerative brain changes and cirrhosis of the liver is named after the man who wrote a classic description of it in 1912 under the title Progressive Lenticular Degeneration A Familial Nervous Disease Associated with Cirrhosis of the Liver Wilson s description is so thorough and meticulous that a student should find the perusal of this thesis both interesting and instructive As a matter of fact the subsequent literature add little to the clinical description or to the pathology of the nervous system The disease had been observed by others more than o years before Wilson but under different names however their descriptions were incomplete (Gowers 1888 Ormerod 1890)

Hepatolenticular degeneration is a chronic familial but non hereditary disease commencing in youth and progressing over a period of years to a fatal termination It is characterized clinically and pathologically by signs of basal ganglia degeneration and cirrhosis of the liver in varying proportions and pigmentation of Descemet s membrane of the limbus of the cornea (Kayser Fleischer Ring)

Etiology

Since Wilson s disease is rare it would be relatively unimportant except for this peculiar combination of brain disease and liver disease which brings to the foregound the problem of the relationship of diseases of these two organs This relationship could be clarified by answering the following questions (1) does the liver disease result in the central nervous system degeneration in Wilson s disease? ( ) does the

brain degeneration result in the liver disease? (3) are the two systems involved by a common factor? (4) does liver disease in general cause brain damage and if so how?

In the older literature hereditary syphilis was regarded as the cause of this disease but Wilson correctly rejected this hypothesis While the disease is not congenital its strangely familial tendency suggests some congenital defect which is aggravated by an exogenous or endogenous toxin

1 *Cerebral Injury Secondary to Hepatic Disease*

The theory that the brain injury is secondary to the hepatic disease was strengthened by the observations of Waggoner and Malamud and more recently by the observations and excellent review of Baker This theory is supported by clinical and experimental observations that demonstrate cerebral disturbances both functional and anatomical following severe hepatic injury (Also see page 411)

In clinical hepatic necrosis cerebral symptoms almost invariably enter the picture when the hepatic changes become grave Thus character changes lethargy somnolence stupor maniacal outbursts and finally coma (hepatic coma) follow in rapid succession in most cases of hepatic failure regardless of its cause The cerebral symptoms herald the gravity of the hepatic disease

Infectious hepatitis In patients dying from infectious or homologous serum hepatitis anatomical changes in the central nervous system have been observed These consist of lymphocytic infiltration around the meningeal vessels as well as in the basal nuclei brain stem and around the ventricles Petechial hemorrhages are scattered through the brain and occasionally gross hemorrhages have been observed

Other diseases involving liver and brain The involvement of the central nervous system in other hepatic diseases is interesting and emphasizes this relationship Among these should be mentioned Weil's disease and other leptospiroses which attack the meninges as well as the liver Hemochromatosis on occasion may show cerebral involvement as well as the characteristic hepatic disease The most interesting observation in this respect is that by Brouwer who described a patient in whom hemochromatosis and Wilson's disease coexisted Waggoner reported a patient with hemochromatosis who showed clinical as well as anatomical changes akin to those of Wilson's disease In erythroblastosis fetalis the involvement of the basal ganglia in the form of kernicterus is commonly seen in the fatal form of this disease

Experimental observations The involvement of the central nervous system in hepatic injury was noted experimentally by Hahn in 1893 This worker observed nervous symptoms in dogs with Eck fistulas who were placed on meat diets This was confirmed by other observers (Fuchs 1921 and Baló and Korpassy 1932) and in addition to ataxia tremors and coma histological cerebral changes compatible with encephalitis were found The feeding of guanidine to cats with Eck fistulas resulted in severe cerebral symptoms The observations of De Jong in experimental catatonia again showed the dependence of certain types of brain injury on hepatic injury

These experimental observations suggest the pathway by which hepatic damage may result in cerebral injury The liver purifies the blood coming to it from the intestines Chemical and bacterial toxins reaching the liver in a normal animal are removed or detoxified In the damaged liver this process is carried out poorly or not at all and the toxins from the intestines reach the brain and produce their destructive effect The possibility also exists that a damaged liver may actively produce a toxin which is injurious to the brain

One cannot deny that in severe hepatic injury cerebral injury does occur and this may be due to (1) a toxin from the intestines not detoxified by the liver, (2) a toxin elaborated by the liver or (3) the absence of a substance necessary for cerebral metabolism which is elaborated by the normal liver In infectious diseases such as Weil's disease the organism itself attacks the meninges while in viral hepatitis the cerebral injury is more likely the result of non specific factors But even when these principles are accepted it does not necessarily follow that in Wilson's disease the brain injury is secondary to the hepatic involvement

Brain injury in Wilson's disease not secondary

to liver damage The most important facts that militate against the theory that in Wilson's disease the brain injury is secondary to liver disease are the lack of correlation between the severity of the liver disease and cerebral involvement and the lack of evidence that the hepatic disease precedes the cerebral disease In most instances the cerebral involvement is most conspicuous and may become advanced to the point of killing the patient and yet the hepatic disease remains minimal latent or subclinical On the other hand an occasional patient will show evidence of advanced cirrhosis with minimal cerebral symptoms If the hepatic dysfunction were the initiating factor of the cerebral disease one would expect a parallelism between the two The degree of hepatic involvement influences the hepatic but not the nervous manifestations of the disease (Herz and Drew)

The liver disease rarely precedes the cerebral disease Although three of Wilson's twelve patients gave a history of icterus long before the cerebral symptoms developed there is no assurance that even in these cases there was progressive liver disease throughout this period of time As a general rule there is no preceding history clinical or laboratory evidence of liver disease

Brain injury is secondary to liver injury in classical liver disease On the other side of the picture is the cerebral involvement in the ordinary type of liver disease which occurs only in advanced liver disease Moreover the cerebral changes differ from those seen in Wilson's disease and even in fatal liver disease are not uniformly present Waggoner and Malamud's study is a notable exception to this They found brain changes in five patients with fatal cirrhosis similar in some respects to those found in Wilson's disease Some of the anatomical findings even in this group differed from the typical findings of Wilson's disease Baker found extensive cerebral changes in only eight of eighteen fatal cases of liver disease These changes consisted chiefly of perivascular demyelination and nerve cell damage

In chronic liver disease central nervous system signs and symptoms especially those analogous to Wilson's disease are extremely rare If one weighs objectively the entire array of evidence it is difficult to maintain that in Wilson's disease the cerebral involvement is secondary to the hepatic disease

2 *Brain Disease Resulting in Liver Disease*

The reverse of the first theory is that the brain disease is primary and this results in secondary hepatic disease While this is one of the oldest theories it could be more easily defended on clinical grounds The preponderance of cerebral symptoms and the late appearance of mild hepatic dysfunction would fit in with this concept The damage to the brain according to this theory results in an atrophic effect on the liver To this may be added the interference with the nutritional state of the patient Roosen Runge examined 45 livers of mongoloid patients and found considerable fatty infiltration and moderate fibrosis The frequency of fatty infiltration in this group was 63% or twice as high as among another group of mentally deficient patients These pathologic changes may be attributed to the hypopituitarism and hypothyroidism characteristic of mongoloid individual rather than the cerebral disease Cirrhosis has not been observed in other chronic cerebral disease and therefore this theory of the pathogenesis of Wilson's disease is no longer seriously entertained

3 *Common Toxin Affecting Liver and Brain*

The possibility of a common toxin damaging both the liver and brain was proposed by Wilson as the cause of the disease This theory would satisfy many of the objections raised against the other theories The more rapid disintegration of the brain as compared to the liver could be explained on the basis of the greater vulnerability of the brain In the exceptional case the liver may carry the brunt of the toxin

But where would the toxin come from and what is its nature? It has even been postulated that the toxin is elaborated in the liver and in turn damages the liver as well as the brain Oddly enough manganese chloride injected into experimental animals causes hepatic cirrhosis and cerebral damage simulating Wilson's disease (Mella 1924 Edsall 1919 Findlay

1924) There is no clinical or biochemical evidence that these patients are victims of manganese poisoning

4 *Aminoaciduria as the Cause of Hepatic and Cerebral Damage*

Uzman and his associates in two provocative papers in 1948 and 1952 reported increased amino acid excretion in patients with Wilson s disease as well as in asymptomatic members of their families The aminoaciduria has been confirmed by others (Cooper et al Cummings) This is an important clue to the possible etiology of this disease The familial incidence as well as the onset in youth or childhood suggests an inborn metabolic defect This defect appears to consist of a persistent loss of amino acids which has the following features (1) it does not depend on lowered renal threshold (2) it is independent of hepatic injury (3) it is not dependent on the protein intake (4) is not accompanied by elevation of blood amino acids (5) there is no specific pattern to the type of amino acids excreted (6) the aminoaciduria varies depending on the duration of the disease

The persistent aminoaciduria which was demonstrated in normal siblings indicates that this defect precedes the development of cirrhosis and may actually be the cause of it The constant loss of protein in the urine may result in protein depletion and consequent nutritional cirrhosis This however would in itself be insufficient to explain the cerebral changes unless one postulates another unknown metabolic defect which results in the cerebral damage Uzman and Hood noticed in several of their subjects an increased excretion of dicarboxylic amino acid peptides From this they postulated a possible deficiency of dicarboxylic-carboxypeptidases in the tissue with resulting increased filtration of these peptides through the glomeruli The renal tubules in their attempt to resorb the peptides lose some amino acids This enzyme deficiency may therefore be responsible for the aminoaciduria as well as the cerebral degeneration This hypothesis would also explain the lack of increased excretion of amino acids when amino acids are injected intravenously or protein is ingested in large amounts

5 *Disturbance in Copper Metabolism as the Cause of Wilson s Disease*

In 1925 Mallory attempted to demonstrate an etiologic relationship between portal cirrhosis and copper intoxication The recent evidence points to a disturbance of copper metabolism in Wilson s disease (1) the brain and liver of patients dying from this disease contain excessive amounts of copper (Cummings, 1948 Spillane et al 1952) (2) urinary excretion of copper is increased (Denny Brown and Porter 1951) (3) serum copper level is abnormal (Glazebrook) (4) the characteristic Kayser Fleischer ring contains copper

Scheinberg and Gitlin studied the ceruloplasmin content of the blood of normal individuals and patients with Wilson s disease Ceruloplasmin is an alpha globulin containing 0 34 % copper This protein was found in very low concentration in patients with Wilson s disease The ceruloplasmin of patients with hepatic cirrhosis was found to be normal They postulate that a congenital defect in the elaboration of this protein is present in Wilson s disease This leads to a disturbance of copper metabolism which may in some way be responsible for the development of this disease There is probably an increased absorption of copper in these patients—above the normal of 1–2 mg per day The disturbance in copper metabolism in this disease may be analogous to the disturbance of iron metabolism in hemochromatosis The relationship of these two diseases is emphasized by the observation of their coexistence in some individuals

It is apparent from the above observations that at least two metabolic defects exist in patients with Wilson s disease These defects are both related to protein metabolism one of these depends upon an enzyme deficiency resulting in aminoaciduria and the other depends on a defect in protein synthesis and results in abnormal copper metabolism

Etiology—Summary

1 Cerebral Injury Secondary to Hepatic Disease (evidence is against this)

a cerebral changes precede hepatic changes

b hepatic disease may remain mild to the end
c in severe hepatic disease (cirrhosis) cerebral damage may be absent
d cerebral damage in fatal liver disease is not the same as in Wilson s disease

2 Brain Disease Results in Liver Disease (points in favor of this)
a brain disease precedes liver disease
b brain disease is usually far advanced when liver disease is noted
c nutritional interference resulting from severe brain disease may result in liver disease
d liver disease has been noted in other cerebral diseases

3 Common Toxin Damages Both Organs
a endogenous toxin originating in liver?
b exogenous toxin —manganese— damages both systems

4 Aminoaciduria as Cause of Disease
a aminoaciduria demonstrated in patients and siblings
b aminoaciduria precedes development of disease
c dicarboxylic amino acid peptides are excreted in urine
d dicarboxylic carboxypeptidase deficiency may be responsible for both

5 Copper Metabolism Disturbance as Cause of Disease
a ceruloplasmin—copper carrying serum protein is decreased
b serum copper level is low or high
c urinary copper is increased
d brain and liver of these patients contains excessive amounts of
e copper
f Kayser Fleischer ring contains copper

PATHOLOGY

The characteristic pathological feature of this disease is the selective lesions of the corpus striatum and the cirrhosis The interesting features about the nervous system involvement is not only the localization of the lesion but its bilateral symmetrical distribution

Nervous System Lesion

The lesions in the brain are confined chiefly to the corpus striatum The degeneration is most marked in the putamen but the globus pallidus and the caudate nuclei are involved to a lesser extent The adjacent optic thalamus escapes untouched The degree of disintegration of these structures varies from discoloration to sponginess to atrophy to excavation and cyst formation These degenerative changes are most marked in the lenticular nucleus while the neighboring structures are involved to a lesser extent

Histologically one sees marked destruction of nerve cells and their processes which are replaced by glial cells The glial overgrowth is very conspicuous and this results in the formation of giant cells of the type referred to as Alzheimer I cells Fat granule cells may invade the degenerated area If there is just glial proliferation and no necrosis the structures are shrunken If disintegration occurs the area becomes spongy and cystic Inflammatory cells are conspicuous by their absence These changes are confined to the nuclei mentioned above However occasionally mild nerve cell changes and minor glial reaction may be noted in the cerebral cortex cerebellum and red nucleus These minor changes do not refute the selectivity of this curious degenerative process

The liver the other organ constantly involved in this disease is almost always but not invariably smaller than normal It shows marked gross pseudolobulation consisting of nodules of varying size some of them quite large Therefore it falls into the group of post necrotic or toxic cirrhosis rather than portal or Laennec s type of cirrhosis The histologic features of this cirrhosis is not distinctive but shows broad strands of fibrous tissue collapsed reticulum disintegrating liver cells nodules of regenerating liver cells and multiplication of bile ducts

Pathology—Summary

Brain
Gross areas involved
1 Putamen chiefly
2 Globus pallidus and
3 Caudate nucleus to lesser extent optic thalamus escapes
Progressive Changes
1 Discoloration
2 Sponginess
3 Atrophy
4 Excavation
5 Cyst formation
Histologic
1 Destruction of nerve cells
2 Glial proliferation

3 Giant cells (Alzheimer I cells)
4 Inflammatory cells are absent

Liver

Gross

Coarsely nodular cirrhosis (post necrotic)

Histologic

1 Broad strands of fibrous tissue
2 Collapsed reticulum
3 Degenerating parenchymal cells
4 Nodular regeneration
5 Bile duct multiplication

Clinical Features

Incidence

It is a rare disease with only 145 varified cases found in the literature up to 1946 Andre) Most of the reports consist of single or several cases The familial incidence is one of its conspicuous and diagnostic clinical features In spite of its rarity it occurs in several siblings of the same generation It has been reported in identical twins It is definitely not hereditary The aminoaciduria which was found in the nonsymptomatic siblings was absent in the mother (Uzman and Hood) Therefore while the defect may be passed in the genes it is absent in the parents

Age and Sex

The sex distribution appears to be equal It is definitely a disease of youth It has been reported in a child of four but most commonly begins in preadolescents or in young adults Some cases have not come to the attention of a physician until late in the fourth decade of life

Symptoms and Physical Findings

The clinical course of the disease may be divided into two groups the acute and chronic form In the acute form the patient runs a septic fever and has all the features of an infectious illness with marked neurologic symptoms and findings The acute course is fortunately rare and the illness terminates fatally in a matter of a few months

The symptoms and physical findings of the chronic form of the disease (which has been referred to as pseudosclerosis of Westphal) can be divided into those referable to the cerebral or hepatic involvement The central nervous system symptoms are by far the most conspicuous in the majority of patients and may indeed form the only clinical features while the hepatic abnormality must be looked for One hundred and ten of the 145 patients reviewed by Andre showed no clinical evidence of cirrhosis In 18 5% of these cases the cirrhosis was conspicuous clinically and in 5% the hepatic disorder was present without neurological findings

Neurological Features

Kinnier Wilson s masterly description of the neurological picture of this disease should be read by every student interested in this phase of the disease These symptoms vary in different families and in different patients as well as in the same patient at different times But while there are remissions and exacerbations there is a relentless downward progression with eventual complete disability and death of the patient

A tremor may be the only neurologic symptom in the chronic (pseudosclerotic) variety of the disease for a long time This tremor is very characteristic and consists of a flapping movement of the outstretched hands which are alternately flexed and extended at the wrists Occasionally the shoulder joint is involved At the beginning the tremor is increased by voluntary movements (Uzman and Denny Brown) The tremor eventually spreads to involve the legs and also the jaw head and neck Movements of a choreic athetoid or dystonic nature may be present Writing is interfered with and eventually becomes impossible Discoordination and disturbance of equilibrium have been attributed (on clinical grounds) to cerebellar disturbance (Herz and Drew)

Rigidity is the neurological sign next in importance and increases the patient s incapacity The rigidity of the legs interferes with locomotion and maintenance of equilibrium Later the rigidity of the extremities at the elbows knees hips may render the patient helpless The contracture of the hand and wrist resembles that seen in paralysis agitans Rigidity of the facial muscles results in the mask like facial features the frozen smile or

grin and drooling of saliva from the mouth Dysphagia and dysarthria add to the patient's disability The dysarthria may result in the complete loss of speech while the dysphagia results in emaciation and may hasten death

Psychic changes are more apparent than real because of the fixed smile drooling at the mouth and dysarthria Intellectual activity may be maintained for a long time Some true mental deterioration has been observed Emotional instability is evidenced by uncontrollable fits of laughter or crying

Hepatic Features

While the hepatic features are usually latent and the hepatic involvement may become evident only on thorough study these occasionally dominate the clinical picture Sometimes patients give a history of jaundice many years before the development of the neurological symptoms

The hepatic manifestation may consist of only mild dyspepsia bloating and anorexia which could easily be attributed to the nervous system disease It has been also pointed out that the hepatic disorder may subside when the neurological symptoms become dominant

The patient may present himself with full blown cirrhosis with splenic enlargement ascites and edema of lower extremities Prominent periumbilical veins may be a conspicuous feature This may be accompanied by a venous bruit and therefore present the cardinal features of the Cruveilhier Baumgarten syndrome (Wollaeger and Shands) Massive esophageal hemorrhage from varicosities may also be one of the presenting signs

Members of families with nervous manifestations of Wilson's disease should be examined for evidence of cirrhosis for siblings may show the hepatic involvement without the nervous features The division of predominant hepatic lesions in several members of a family and mild nervous manifestation in others were observed by Barnes and Hurst as well as by Lhermitte and Muncie Clubbing of fingers and toes was noted in one patient by Zelman and Gilbert

The Kayser Fleischer ring which consists of a brownish or greenish pigmentation of Descemet's membrane of the cornea is one of the diagnostic signs of Wilson's disease It has been suggested that this pigment is related to urobilin and that it is at least in part dependent on a copper compound When the pigmentation is extensive it can be seen with the naked eye but usually a slit lamp is required for its detection It is not universally present in all forms of the disease In the chronic or pseudosclerotic variety it is detected in 100% of cases but is found in only 60% of the acute form of the disease Its absence in the more rapidly progressive disease can be explained on the basis of insufficient time for its development and its absence does not refute the diagnosis This ring of pigmentation has been demonstrated in cases of cirrhosis that show no other neurological findings and is the sole diagnostic evidence of the true nature of the disease The intensity of this ring of pigmentation may decrease with treatment A sunflower cataract has also been described in this disease

Clinical Features—Summary

Incidence—rare about 150 cases
Familial
Sex—equal distribution
Age—usually begins in preadolescence from 4 to 40
Symptoms
- **Acute Form**
  - **Febrile rapid course**
  - **Marked neurologic changes**
  - **Death in several months**
- **Chronic Form (pseudosclerosis of Westphal)**
  - **Cerebral symptoms most conspicuous or only symptoms**
  - **Motor**
    - **tremor**
      - **flapping movements of hands**
      - **shoulders may be involved**
      - **legs jaw head and neck finally involved**
      - **increased by voluntary movement**
    - **choreic athetoid dystonic movements**
    - **writing impaired**
    - **discoordination and**

else the patient may go on for many years suffering from a tremor which varies in intensity. In these chronic cases the patient may die from bleeding esophageal varices or hepatic failure.

The treatment of the neurological disorder consists chiefly in reduction of the tremor by the use of the various belladonna alkaloids as well as prevention of contractures by orthopedic means and proper nursing care for maintenance of nutrition and body hygiene.

Denny-Brown and Porter reported the use of BAL 1.0 to 1.5 cc. in peanut oil twice a day for ten days every other month. This aids in the mobilization and increases the excretion of copper. They have noted decrease in neurological findings and fading of the Kayser-Fleischer ring in several patients under this treatment. This report suggests that if treatment is started early the changes are reversible.

Another therapeutic approach that may have some measure of success in reversing or delaying the downward trend of the disease is one directed toward the cirrhosis. It is natural therefore that dietary therapy should be emphasized. A high protein, high caloric diet low in fat is therefore advised. Homburger maintained two patients on such diet for 14 to 17 months and noted clinical improvement while a sister who refused dietary therapy went rapidly downhill. Lowering of the high protein diet in one of these patients resulted in deterioration of liver function. Methionine did not enhance the long term favorable effects of the high protein diets. However, if the dietary intake is poor, supplementation with methionine is indicated. Alpha tocopherol should be tried because of the possible value of this agent in postnecrotic cirrhosis and certain forms of nervous disease. This should be used in doses of 100 mg. three times daily orally or parenterally if the oral route cannot be used. Supplementary vitamins of the B complex group should also be administered.

Favorable effect from cytochrome C therapy 80 mg. intramuscularly daily on the neurological and hepatic symptoms of the disease were noted by Zelman and Gilbert in one patient. The rationale of this is based on a presumed disturbance of tissue oxidation. The patient went downhill after discontinuance of therapy but at postmortem much hepatic regeneration was noted which they attributed to the cytochrome C.

Therapy—Summary

Symptomatic
- **Belladonna alkaloids**
- **Orthopedic appliances**
- **Hygienic care**

Specific
- **BAL 1.0 to 1.5 cc. twice a day for ten days every other month**
- **High protein diet supplemented with vitamins**
- **Cytochrome C—80 mg. intramuscularly daily**

75 Von Gierke's Disease, Galactosemia, Fanconi Syndrome

Von Gierke's Disease

This disease known also as glycogen disease, glycogen storage disease hepatomegalia glycogenica hepatonephromegalia glycogenica is one of disturbed glycogen metabolism characterized clinically by its onset in infancy or early childhood with abdominal enlargement hypoglycemia acetonuria and retarded development and pathologically by enormous hepatic and renal enlargement due to excessive glycogen deposits in these organs

Introduction

This disease in spite of its rarity (200 cases reported) is interesting from two aspects Its history dates back only two decades to 1929 when von Gierke described in detail the autopsy of a girl dying at the age of eight from influenza The liver was thrice the normal size and the kidneys twice the normal size (hepatonephromegalia) The other point of interest to physiologist pathologist as well as clinician is that the basis of the pathologic process is the peculiar disturbance of carbohydrate metabolism resulting in abnormal deposition of glycogen of unusual stability in the liver and kidneys In von Gierke s original case the liver contained 10 43% glycogen which decreased but little when incubated for six days at 37°C Although the disease bears von Gierke s name von Creveld and Snapper described a similar case one year before (1928) The hepatic type of this disease will be discussed here although rarely deposition of glycogen principally in the cardiac muscle and sparing the liver makes this disease of cardiological importance (cardiomegalia glycogenica)

Pathogenesis and Pathologic Physiology

The metabolic abnormality consisting of increased deposition of glycogen especially in the liver may be due to

1 increased glycogen synthesis (glycogenesis)
2 abnormal glycogen synthesis (formation of abnormal glycogen)
3 defective or impaired glycogenolysis

There is no evidence whatever for the first assumption With forced feeding it has been possible in animals to produce large glycogen stores in the liver but this glycogen is readily available for the animals metabolic needs but the glycogen in this disease is not

Kimmelstiel claimed that the glycogen formed in this disease differs from normal glycogen He claimed that it was broken down by normal diastase and when this glycogen was broken down by diastase the product differed from the one derived from normal glycogen Neither of these results were confirmed by other investigators Illingworth and Cori found the structure of the glycogen normal in eight out of ten patients with glycogen storage disease

The outstanding and remarkable finding in this disease is the stability of the glycogen in the tissue in vitro This contrasts sharply with the remarkable lability of glycogen in human and animal tissues dying from other diseases Normal liver tissue loses 70 to 100% of its glycogen at 25 C in 48 hours the liver from a patient with glycogen storage disease may lose none of it That this remarkable stability is not due to an abnormal form of glycogen is proved by the fact that incubation with normal liver tissue will result in a rapid decrease of the glycogen The unusual stability of the

glycogen is akin to the situation in the fetus in whom the enzymatic machinery for glycogenolysis is not yet developed.

Further proof that the defect is in the glycogenolytic process was deduced by Mason and Anderson. While normal liver mash reduced the glycogen of the diseased livers, liver mash from these patients were unable to reduce the glycogen from normal animals and man. While an attempt has been made to attribute this defect to a lack of diastase, this has been disproved by finding normal amounts of diastase in these patients' livers, urine and blood.

The defect apparently lies in the phosphatase activity in the liver. Cori and Cori demonstrated the absence or marked decrease of glucose-6 phosphatase in the liver of patients with this disease. This enzymatic defect makes the enormous amount of liver glycogen unavailable for maintaining the normal blood sugar during fasting. This in turn leads to (1) hypoglycemia, which results in convulsions, and (2) increased breakdown of fat to supply caloric requirements with resultant acetonuria. Administration of carbohydrates reverses this process, raises the blood sugar, makes carbohydrate available for metabolic needs, reduces fat catabolism and, with it, the ketonuria is abolished.

The lowered alkaline phosphatase activity of the liver in this disease (Thannhauser et al.) is additional evidence of an enzymatic defect. A glycogen protein combination and abnormal colloidal state in the liver cell have also been considered as factors in the glycogen stability.

The slight or absent rise in the blood sugar after adrenalin injection is another sign of the inability of the liver to break down the glycogen into glucose. In contrast to the lack of response to adrenalin, there is increased response to small doses of insulin (insulin sensitivity).

The prolonged rise of the blood sugar with administration of carbohydrate has been claimed by Mason and Anderson to be proof of a defect in glycogenesis as well as glycogenolysis. However, this is probably a quantitative rather than qualitative defect. These patients react in this respect like individuals who have been on a low carbohydrate diet with a sluggish removal of ingested glucose. Levulose and galactose tolerance tests have been reported to give flat and high prolonged curves. Non-dextrose reducing substances in the urine are thought to be pentose.

Negative nitrogen balance of about 0.3 gm of nitrogen per day has been reported. Normally there is a positive nitrogen balance of 0.2 to 0.3 gm a day; therefore the total nitrogen loss as compared to normal is 0.5–0.6 gm a day. Testosterone failed to cause nitrogen retention.

Pathology

The enormous size of the liver is the conspicuous gross feature. The liver in the autopsied cases has been three to four times the normal size. This organ is smooth, glistening, lighter in color than normal, but not as light as a fatty liver, and is not greasy. The kidneys are enlarged but only about twice the normal size. The heart in the hepatic form of the disease is usually normal in size, but in the cardiac form (cardiomegalia glycogenica) may be enormously enlarged while the liver is normal.

Microscopically, the liver cells are greatly enlarged, cytoplasm is granular, empty looking and stain poorly with eosin. The cells assume a "plant like" appearance. The nucleus is centrally located. Best's carmine stain shows that the cell is laden with glycogen (Fig. 13). The glycogen content of the liver may be as high as 16% of wet weight, and this glycogen does not disappear on standing. The oxygen consumption of this liver tissue is only 12 to 18% of normal tissue because of the enormous amount of inert material. Actually, because of the size of these cells, a gram of liver tissue contains only about 1/10 the normal number of cells. There is usually very little fat in these cells. Yet in von Gierke's original case, fat was reported to be present in greatly increased amounts.

The kidneys on staining with Best's carmine stain shows much glycogen in the cells of the proximal and distal convoluted tubules. Increased glycogen is usually found in striated muscles. The heart in the hepatic form of the disease is either free of glycogen or contains only small amounts. The spleen, pancreas, adrenals, thyroid, parathyroid, pituitary and intestines are free of glycogen.

Etiology

The age of onset is early infancy, frequently the first six months of life, although at times the disease does not come to the attention of a physician until the third year of life. Sex distribution is equal; von Creveld reviewed 43 cases, of these 16 were females and 17 males.

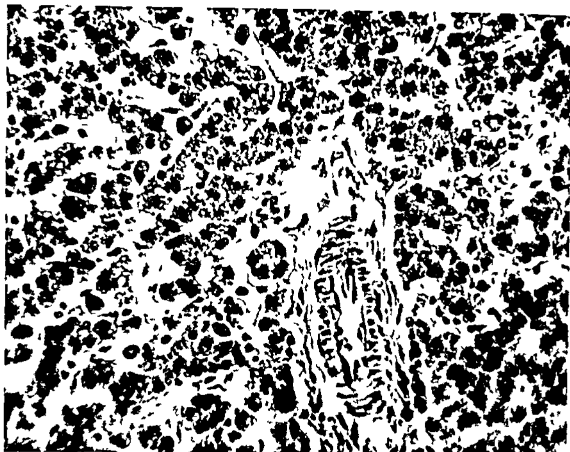


Fig 93 Von Gierke s disease Microsco ic section (X 00) of liver stained with Best s carmine showing the marked increase of glycogen in the liver cells (Courtesy Dr Otto Saphir Department of Pathology Michael Reese Hospital Chicago)

von Creveld s case was a boy Bridge and Holt in 1945 reported two cases one a boy the other a girl Manter and Bowman s case was in a male infant while Mason and Anderson s case was a girl The defect is undoubtedly congenital since its onset is noted so early in life There is a definite familial tendency since the condition has been reported in siblings and even in twins Consanguinuity of the parents of patients has also been reported

Clinical Picture

The infants usually appear normal at first and appear to grow satisfactorily An enlargement of the abdomen is however noticed by *the mother very early The abdominal enlargement* progresses out of proportion to the development of the infant Convulsive seizures may be elicited as part of the early history of these cases Later retarded development as manifested by inability to walk and markedly delayed dentition is noted *Attacks of jaundice* have also been reported in some cases

On examination the striking feature is the markedly enlarged abdomen and well rounded face but very thin and flabby extremities especially the lower extremities There actually may be an increased fat distribution over the abdomen and face The poor muscular development accounts for the inability to walk The liver is markedly enlarged usually it reaches the crest of the ileum and crosses to the left side The edge is sharp firm and smooth but not tender The palpable left lobe of the liver has been *falsely interpreted* as an enlarged spleen Splenomegaly is not found in this disease The peculiar appearance of these children along with their retarded development has at

times led to the diagnosis of an endocrine disturbance But if endocrine abnormalities are present they are not primary but the result of poor nutrition consequent to the disturbed carbohydrate (glycogen) metabolism The mental development is usually normal

The characteristic laboratory findings added to liver biopsy help to close the diagnostic chain Fasting hypoglycemia and acetonuria are characteristic While the normal infant may develop a slight acidosis after a 24 hour fast and no hypoglycemia these patients will show marked acetonuria and a blood sugar as low as 10–15 mg per 100 cc 3 to 4 hours after a meal This marked hypoglycemia accounts for the history of convulsions and coma These findings respond readily to ingestion or injection of glucose

Another diagnostic test is the lack of response of blood sugar to adrenalin injection In a normal individual adrenalin injected subcutaneously results in a prompt rise of the blood sugar In this disease adrenalin typically evokes no or only a slight rise of blood sugar The ingestion of a given quantity of glucose by mouth (glucose tolerance) results in a marked rise of blood sugar to hyperglycemic levels and in several hours a drop to hypoglycemic level Blood glycogen which is normally 13 5 mg % (Bridge and Holt) is usually elevated and in their two cases was 48 and 85 mg per 100 cc Most of this glycogen was found in the leucocytes

Other tests which are not of diagnostic importance but serve to round out the picture can be mentioned Hypercholesterolemia of moderate degree occurs Lipemia has been reported in some cases but is an inconstant feature Although jaundice occurs liver function tests are usually normal Decrease of cholesterol esters to any great extent is not a feature of this disease Protein partition studied by von Creveld was found to be normal The total protein may occasionally be low—5 4 gm per 100 cc (Bridge and Holt) These authors also report an alkaline phosphatase of 17 4 Bodansky units in their case Occasionally urobilinogenuria is present Flocculation tests are usually normal The blood may show a slight anemia and mild leucopenia

Course and Prognosis

Von Creveld s two cases remained in good health until adolescence and early childhood (boy 18 girl 10) From this experience he concluded that the prognosis is not necessarily poor Worster Draught s girl was in good health and normally developed at the age of 25 (liver normal in size) This case suggests that the metabolic abnormality may eventually be overcome if the patient survives long enough However as a rule immaturity poor development and retarded dentition persist

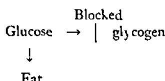
It also appears in spite of von Creveld s statement to the contrary that these children have a low resistance to infection and frequently succumb to respiratory infections Their lack of resistance may be explained partially on the basis of impaired function of the leucocytes which are laden with 10% glycogen Death may occur in early infancy

Diagnosis and Differential Diagnosis

The diagnosis is based on finding in an infant or young child (1) an enormously enlarged liver (2) fasting hypoglycemia and ketosis (3) no rise in blood sugar after adrenalin injection and (4) liver biopsy showing much glycogen which does not disappear on standing The diseases that it may have to be differentiated from are (1) infantile cirrhosis (2) the reticulo-endothelioses (Gaucher s Niemann Pick s disease) (3) tumors of the liver (4) congenital hypertrophic steatosis and (5) galactosemia In the first condition jaundice may be an important feature disturbed liver function is a frequent finding Splenic enlargement is found in 1 and especially in 2 In the reticulo endothelioses the splenic enlargement is more conspicuous than the hepatic enlargement Tumors of the liver can frequently be surmised from the irregularity of the hepatic enlargement In none of these are the metabolic disturbances characteristic of glycogen disease found

Congenital hypertrophic steatosis is an exception to this In this congenital metabolic disturbance with enormous accumulation of fat in the liver there may be hypoglycemia and lack of response to adrenalin This in addition to the large smooth liver may complete the

illusion of glycogen disease. As a matter of fact the common term "hypertrophies polycorigues" has been applied to glycogen storage disease and the hypertrophic steatosis. The clinical dissimilarities of hypertrophic steatosis are as follows: (1) nutritional disturbances, poor intake of food are noted before the disease becomes established; (2) febrile episodes are frequent, infection and nutritional disturbances may be the etiologic factors in the fatty metamorphosis; (3) acetonuria is rare; (4) hyperlipemia may be present; and (5) jaundice may be marked. This disease may be due to metabolic defect in which glucose cannot be converted to glycogen (aglycogenesis) and therefore is stored as fat.



Galactosemia is diagnosed by identifying galactose in the urine; albuminuria is a common feature of this disease.

Treatment

Specific therapy is lacking.

Large doses of amylase orally and by injection have been found ineffective. There is some evidence that x-ray therapy of the liver may be beneficial and should be given a trial. Therapy may be directed successfully against the most troublesome physiologic disturbance, namely, the hypoglycemia with convulsions and acidosis. For this frequent feedings are helpful *and tend to prevent the fasting hypoglycemia*. A high protein meal consisting of ground beef given late at night has been shown by Bridge and Holt to prevent the early morning ketosis. *In one patient the hypoglycemia* and acetonuria responded to adrenocorticotropin (ACTH) injections (Langewisch and Bigler).

Summary

Findings

Clinical features

1. **Obesity of face and abdomen and thin extremities**
2. **Liver greatly enlarged, spleen normal**
3. **Fasting hypoglycemia and ketonuria**
4. **Epinephrine → no rise in blood sugar**

Pathology

1. **Liver cells filled with glycogen (Best's carmine stain)**
2. **Glycogen (abnormally stable) does not disappear on standing**
3. **Glycogen in renal tubules**

Treatment

1. **X-ray to liver**
2. **Frequent, high protein feedings**
3. **Adrenocorticotropic hormone**

Galactosemia

Galactosemia (galactosis, galactose diabetes, chronic galactemia and chronic galactosuria) is an inborn error of galactose metabolism *occurring in infants and children and* accompanied by retarded development, hepatomegaly, galactosuria and albuminuria.

Incidence

It is a very rare disease, first described by Reuss in 1908. Bray and his associates reported three cases and found only 14 other proven cases in the literature up to 1952. An additional case was reported by Langewisch and Bigler in 1952.

Etiology

It is a congenital and familial metabolic disturbance involving a defect in the conversion of galactose to glucose. Since it is thought that genes control specific biochemical reactions, it follows that the disease is caused by a change in, or absence of a gene controlling this particular process. It has been suggested that changes in the liver seen in this disease are due to a toxic effect of galactose on the liver. It is hard to see how a normal constituent of the diet should assume toxic properties. Since the liver is the principle site for conversion of galactose to glucose, it is more logical to speculate that a peculiar type of hepatic damage precedes and results in this defect in conversion. There must be a specific and unique change in the liver cells since the known types

of liver damage do not produce such marked galactosuria

Pathology

The changes in the liver are of particular interest Diffuse fibrosis focal necrosis and lymphocytic infiltration have been described Fatty infiltration has been described and in several instances changes compatible with portal cirrhosis accompanied the fatty metamorphosis Glycogen is demonstrable in the liver cells

Clinical Features

Vomiting after milk feedings are noted very early and this is followed by loss of weight and signs of defective mental and physical development Jaundice has been described in several cases Hepatomegaly is a conspicuous sign Cataracts are frequently detected The symptoms and signs abate with the reduction of galactose or its exclusion from the diet

Laboratory Features

Urine contains small amounts of reducing substance which on fermentation or paper chromatography is proven to be galactose The galactosuria increases with increased ingestion of galactose Albuminuria and cylindruria are also present Glucose tolerance tests give normal curves Galactose tolerance tests result in prolonged elevation of blood galactose for as long as seven hours Liver function tests may show slight deviation from the normal Positive cephalin cholesterol flocculation tests have been mentioned Hyperbilirubinemia may be present and I should expect the bromsulphalein test to be abnormal

Prognosis and Treatment

The cirrhosis in this condition seems to be of a benign type and perhaps is even reversible with general improvement of the patient Reduction of galactose intake is the major therapeutic approach Increased glucose intake results in an increased tolerance for galactose As time goes on the galactose tolerance also improves

Galactosemia—Summary

Etiology
- **Inborn metabolic error**
- **Familial**
- **Defect may reside in liver**

Pathology
- **Liver may show**
  - **Fibrosis**
  - **Focal necrosis**
  - **Lymphocytic infiltration**
  - **Fatty changes and**
  - **Cirrhosis**

Clinical Features
- **Vomiting**
- **Loss of weight**
- **Retarded mental and physical development**
- **Jaundice**
- **Hepatomegaly**
- **Cataracts**

Laboratory Features
- **Galactosuria**
- **Albuminuria**
- **Glucose tolerance normal**
- **Galactose tolerance abnormal**
- **Liver function tests show slight deviation**

Fanconi Syndrome

This is a peculiar syndrome originally described in children but also occurring in adults characterized by intractible hypophosphatemic rickets renal glycosuria aminoaciduria and cirrhosis of the liver

Incidence

Although the syndrome was first described by Schier and Stern in 19 6 it carries the name of Fanconi who described it more thoroughly in 1931 In 1943 McCune and co-workers collected 39 cases in the literature and other cases have been reported since then

Etiology

Heredity definitely seems to play a role in this syndrome but the exact type of inheritance has not been determined Stowers and Dent suggest that it may be a dominant characteristic in the adult type and recessive in the childhood type The theory of sex linkage lacks support but consanguinuity has been uncovered in the history of several young patients Consanguinuity is not so conspicuous among the adult patients

Age While predominately a disease of in

fancy and childhood the syndrome has been recognized in adults. The earliest age of onset reported is eight days and many of the cases begin in infancy. However Hunter recognized the syndrome in an adult and the patient reported by Stowers and Dent was 34 years of age. The disease is equally distributed between the sexes.

Pathogenesis

The pathogenesis of this curious syndrome seems to depend upon a metabolic or enzymatic disturbance and the seat of this disturbance may be the renal tubule. The rachitic changes in the bone are not dependent on a lack of vitamin D and do not respond to it. The abnormalities in this disease seem to result from the loss of phosphates glucose and amino acids in the urine. This increased excretion may be due to failure of tubular resorption since the blood levels of these substances are not increased. The chronic tendency to acidosis existing in this disease lowers the renal threshold for phosphates. Phosphate glucose and amino acids are resorbed chiefly in the proximal convoluted tubules and the lack of phosphate here may interfere with phosphorylation which, in turn interferes with the absorption of these substances.

The loss of phosphates is therefore dependent upon the acidosis and the lowered renal threshold for this substance. The loss of phosphates is accompanied by an increased loss of calcium which leads to osteomalacia. The persistently alkaline urine that these patients excrete results in a local chronic alkalosis which may further damage the renal tubules. The increased calcium excretion accentuates this renal damage.

Its tempting to attribute the hepatic cirrhosis to the persistent aminoaciduria albeit the hepatic lesion is not constant in this syndrome but when it occurs it is undoubtedly due to an allied metabolic disturbance. Methionine and cystine deficiencies which are known to result in experimental cirrhosis cannot be implicated in this disease since these amino acids are not excreted in the urine. This does not exclude the possibility that there is some disturbance of their utilization by the tissues.

Excess of serine in the urine of Stowers case suggests impaired cystine synthesis but the normal sulfur excretion in that patient speaks against this hypothesis. However pathological deposits of cystine in various tissues as well as the liver has been observed, and occasionally cystinuria is also observed. The cystine crystals deposited in the liver have been accused as a source of irritation and a stimulus to cirrhosis (McCune et al 1943). The gross deposits of cystine in the tissue suggests non utilization of this important amino acid. The loss of this amino acid whether by inanition, loss in the urine or loss into inert aggregates in the tissues would result in liver damage.

Dent has reported an increase of α amino n butyric acid in the urine after oral administration of methionine which was more marked than in normal individuals. While the significance of this observation is not clear it suggests some abnormality in methionine metabolism. It is therefore reasonable to conclude at the present stage of our knowledge that in Fanconi s syndrome the cirrhosis of the liver is probably dependent upon an abnormality of protein and amino acid metabolism.

Pathology

Liver Abnormality of the liver while not a universal feature in this syndrome nevertheless occurs in over half of the reported cases. Of 1 cases in the literature in which anatomic data is available five showed normal livers. Of the other seven two showed a frank cirrhosis four focal necrosis and one a fatty liver. The case reported by Stowers and Dent showed a marked cirrhosis. The cirrhosis is of the post necrotic type and shows marked nodular hyperplasia with extreme distortion of the organ. The right and left lobes are not involved to the same extent. Microscopically the necrosis is seen to be centrolobular in addition active regeneration leucocytic infiltration and broad strands of fibrous tissue are seen completely distorting the architecture. Large pale intranuclear inclusion bodies in the normal looking cells have been observed. The exact nature of these inclusion bodies has not been determined. In the cases showing only focal necrosis deposits of cystine crystals (cystinosis) were observed and were held responsible for the focal necrosis on a mechanical basis. A primary malignant hepatoma was found in Stower s case indicating this peculiar cirrhosis may also result in hepatic malignancy. The spleen is usually enlarged when cirrhosis is well developed.

Kidneys The anatomic changes in the kidneys are of particular interest in view of the central position of this organ in the pathogenesis of this syndrome Grossly the kidneys may be slightly enlarged b t otherwise not remarkable The chief histologic alterations are located in the renal tubules and are extremely variable The tubules have been described as dilated with flattened epithelium or blocked by swollen epithelial cells Fatty deposits fibrosis and deposits of crystals probably cystine have been described All but one autopsied patient showed renal tubular changes Obliteration of glo meruli and cuboidal glomerular endothelium have been noted

Skeleton The bones show marked osteoporosis d rangements of periosteal and endochondral ossifi cation diagnostic of infantile rickets as well as fibroblastic changes in the spongy and compact layers of the long bones suggestive of hypopara thyroidism are seen m croscopically The para thyroid however is normal in most cases and in a few instances shows mild gross enlargement with normal cellular structure No significant abnormali ties were noted in other endocrine glands

Fanconi Syndrome—Summary

Etiology
- Heredity important
  - dominant or
  - recessive
  - consanguinity plays a role
- Age
  - Predominance in children
  - Adult type occurs
- Sex
  - Equal distribution

Pathogenesis
- Renal tubules, seat of enzymatic defect resulting in loss of
  - a phosphates
  - b glucose
  - c amino acids
- Acidosis leads to
  - Increased loss of phosphates leads to



Phosphorylation defect which leads to	Loss of cal cium leads to
Glucose and	Osteomalacia
Amino acid loss	
Alkaline urine	

- Increased calcium excretion leads to further renal damage
- Cirrhosis result of disturbed amino acid metabolism

Pathology
- Liver
  - Changes in about half of the cases
  - Cirrhosis of post necrotic type
  - Microscopic changes
    - centrolobular necrosis
    - regeneration
    - leucocytic infiltration
    - broad strands of fibrous tissue
    - cystine crystal deposits
- Spleen enlarged
- Kidneys enlarged
  - Microscopic changes in renal tubules
    - dilated
    - flattened epithelium
    - fatty changes
    - fibrosis
    - cystine crystals
- Skeleton
  - Marked osteoporosis with changes suggestive of
    - infantile rickets and
    - hypoparathyroidism

Clinical Features

The symptoms usually appear in the first two yea s of life and consist of anorexia loss of weight poor skeletal and muscular develop ment gross skeletal changes polyuria and bouts of fever Spontaneous fractures may occur X ray of the long bones reveal the char acteristic changes of rickets The nature of the abnormality becomes evident from the poor response to vitamin D The polyuria and thi st may be intense The dehydration from the relentle polyuria is thought to be responsible for the bouts of fever

In the adult patient described by Stowers and Dent symptoms referable to the skeleton were likewise pre ent These consisted of per sistent backache and radiation of pains into both thighs Clinically and roentgenographi cally one may find evidence of old rickets The liver and spleen may be palpable if cir rho is is present

Laboratory Findings

The laboratory studies yield the most s gnifi cant data in this disease

Glycosuria is usually continuous but in some

has been described as intermittent and is accompanied by a normal blood sugar. Hypoglycemic reactions have been induced in these patients because they were erroneously treated as diabetics. Abnormal glucose tolerance curves have been described but they are of questionable reliability.

Aminoaciduria is the other characteristic feature of this syndrome. The daily urinary amino acid nitrogen is about 1.0 gm compared to normal of 0.1 to 0.4 gm (Dent 1947). The following amino acids have been identified in the urine in abnormal amounts: aspartic acid, glutamic acid, glycine, serine, alonine, threonine, valine, leucine, isoleucine, tyrosine, arginine, hydroxyproline, phenylalanine. Histidine and aminobutyric acid were present in smaller but nevertheless abnormal amounts. Urinary sulfur was present in normal amounts. The aminoaciduria, like the glycosuria, was present in spite of normal blood levels. There seems to be a parallelism between the degree of glycosuria and aminoaciduria.

Phosphaturia of marked degree which may exceed the total phosphorus absorbed is another salient urinary finding. Other urinary findings are albuminuria and mild pyuria and occasional hematuria. The urinary pH is usually near the neutral side of the scale.

The important chemical abnormalities of the blood are the hypophosphatemia of 1 to 3 mg % and the acidosis with a CO combining power of about 30 volume %. Several cases with hyperphosphatemia and cystinosis have been reported. The serum calcium is usually normal or slightly reduced. This reduction is occasionally sufficient to result in tetany.

The liver function tests may remain normal in spite of an advanced cirrhotic process. Liver biopsy should therefore be of help to determine the status of the liver antemortem.

Kidney function tests may show no or mild abnormality. The cases with hyperphosphatemia showed azotemia.

Laboratory Features—Summary

Glycosuria with
Normal blood sugar

Aminoaciduria
- **Amino acid N 1.0 gm daily**
  - **aspartic acid**
  - **glutamic acid**
  - **glycine**
  - **serine**
  - **alanine**
  - **threonine**
  - **valine**
  - **leucine**
  - **isoleucine**
  - **tyrosine**
  - **arginine**
  - **hydroxiproline**
  - **phenylalanine**

Normal Amino acid Blood Levels

Other urinary findings
- **phosphates**
- **albuminuria**
- **cylindruria**
- **pyuria**
- **hematuria**
- **pH neutral or alkaline**

Other Blood findings
- **phosphorus decreased 1-3 mg %**
- **CO_2 combining power decreased 30 vol %**
- **calcium normal or slightly reduced**

Liver Function Tests Normal or slightly altered

Prognosis and Treatment

While the prognosis is generally poor, the fact that some of these patients survive to adulthood is an indication that the syndrome should not be regarded with complete pessimism. High potassium intake apparently results in increased phosphorus and calcium retention as well as reduction in acidosis. While the rickets is unquestionably resistant to vitamin D, large doses of this vitamin may have some effect. High protein diet is indicated to counteract the loss of protein in the urine and may help to forestall the development of cirrhosis. The usefulness of isolated amino acids such as methionine has not been determined.

76—Lipidosis

THE lipidoses are a group of diseases in which the essential disturbance is in the lipid metabolism Since the seat of this disturbance is not necessarily in the liver they cannot be considered liver diseases however it is relevant to discuss them at least briefly here for three reasons (1) the liver plays a role in lipid metabolism (2) the liver is one of the organs secondarily involved in some of these diseases and (3) some of the clinical and chemical features of these diseases are similar to those seen in primary hepatic disease While these diseases will be discussed briefly here for a more complete description the reader is referred to the monograph by Thannhauser

The role of the liver in the various phases of lipid metabolism has been discussed in several sections of the book and one should logically look to the liver in the presence of disturbed lipid metabolism But only in biliary cirrhosis is the hypercholesterolemia definitely secondary to hepatic disease while in the other syndromes in this group the liver is not a factor in their pathogenesis but is involved secondarily When the liver becomes secondarily involved it is likely that this organ contributes to the metabolic disturbance

One clinical feature that some of these diseases have in common is the cutaneous xanthoma The xanthomatoses (diseases showing cutaneous xanthomas) are classified by Thannhauser into three groups according to the serum lipid level

1 Hypercholesterolemic xanthomatoses
2 Hyperlipemia with secondary eruptive xanthoma
3 Normacholesteremic xanthomatoses

In the first group the xanthomas are accompanied by increased levels of serum cholesterol Xanthomatous cirrhosis belongs in this group the xanthomas and hypercholesterolemia are secondary to the biliary obstruction There is an essential or familial type of hypercholesterolemic xanthomatosis The hypercholesteremia of hypothyroidism and nephrosis is not accompanied by xanthomas

In the second group there is a hyperlipemia consisting of neutral fats this hyperlipemia may be familial or idiopathic or be secondary to pancreatic disease either diabetes or chronic pancreatitis

In the third group xanthomas occur in spite of a normal serum cholesterol Eosinophilic granuloma and the so-called Schuller Christian syndrome fall into this group

FAMILIAL OR HEREDITARY HYPERCHOLESTEREMIA

This familial disturbance of cholesterol metabolism occurs clinically in two forms with and without cutaneous xanthoma Those without xanthomas are also referred to as the forme fruste of the hypercholesteremic familial xanthomatoses The hypercholesteremia is usually not high If a serum cholesterol of 350 mg per 100 cc or higher occurs in three or more members of one family it is classified as hereditary hypercholesteremia (Adlersberg et al) The cutaneous lesion may consist of xantholesma xanthoma tuberosum xanthoma planum xanthoma tendinosum and xanthoma of internal organs blood vessels endocardium and bile ducts

Incidence

It is not a rare condition if one uses the above criterion and was found in 5.5% of individuals surveyed by Adlersberg and coworkers They found no instance of hereditary hypercholesteremia in Negroes The incidence in 104 Jewish families was 10.6% while in 9[illegible] non Jewish families it was only 1%

has been described as intermittent and is accompanied by a normal blood sugar. Hypoglycemic reactions have been induced in these patients because they were erroneously treated as diabetics. Abnormal glucose tolerance curves have been described but they are of questionable reliability.

Aminoaciduria is the other characteristic feature of this syndrome. The daily urinary amino acid nitrogen is about 1.0 gm. compared to normal of 0.1 to 0.4 gm. (Dent, 1947). The following amino acids have been identified in the urine in abnormal amounts: aspartic acid, glutamic acid, glycine, serine, alonine, threonine, valine, leucine, isoleucine, tyrosine, arginine, hydroxyproline, phenylalanine. Histidine and aminobutyric acid were present in smaller but nevertheless abnormal amounts. Urinary sulfur was present in normal amounts. The aminoaciduria, like the glycosuria, was present in spite of normal blood levels. There seems to be a parallelism between the degree of glycosuria and aminoaciduria.

Phosphaturia of marked degree which may exceed the total phosphorus absorbed is another salient urinary finding. Other urinary findings are albuminuria and mild pyuria and occasional hematuria. The urinary pH is usually near the neutral side of the scale.

The important chemical abnormalities of the blood are the hypophosphatemia of 1 to 3 mg. % and the acidosis with a CO_2 combining power of about 30 volumes %. Several cases with hyperphosphatemia and cystinosis have been reported. The serum calcium is usually normal or slightly reduced. This reduction is occasionally sufficient to result in tetany.

The liver function tests may remain normal in spite of an advanced cirrhotic process. Liver biopsy should therefore be of help to determine the status of the liver antemortem.

Kidney function tests may show no or mild abnormality. The cases with hyperphosphatemia showed azotemia.

Laboratory Features—Summary

Glycosuria with
Normal blood sugar
Aminoaciduria
Amino acid N 1.0 gm. daily
- **aspartic acid**
- **glutamic acid**
- **glycine**
- **serine**
- **alanine**
- **threonine**
- **valine**
- **leucine**
- **isoleucine**
- **tyrosine**
- **arginine**
- **hydroxiproline**
- **phenylalanine**

Normal Amino acid Blood Levels
Other urinary findings
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- **pH neutral or alkaline**

Other *Blood* findings
- **phosphorus decreased 1–3 mg. %**
- **CO_2 combining power decreased 30 vol. %**
- **calcium normal or slightly reduced**

Liver Function Tests Normal or slightly *altered*

Prognosis and Treatment

While the prognosis is generally poor, the fact that some of these patients survive to *adulthood is an indication that* the syndrome should not be regarded with complete pessimism. High potassium intake apparently results in increased phosphorus and calcium retention as well as reduction in acidosis. While the rickets is unquestionably resistant to vitamin D, large doses of this vitamin may have some effect. High protein diet is indicated to counteract the loss of protein in the urine and may help to forestall the development of cirrhosis. The usefulness of isolated amino acids such as methionine has not been *determined*.

first thoroughly described by Buerger and Grutz in 193- and therefore their names are frequently attached to it

Etiology

The cause of the disease is unknown but it is probably a congenital and familial metabolic disturbance involving transportation utilization and deposition of fat The familial and hereditary nature was suggested by the report by Holt and associates of idiopathic hyperlipemia in an eleven year old girl whose mother and three brothers were similarly effected No known hormonal or dietary deficiency has been demonstrated A similar type of hyperlipemia can occur as a result of the metabolic disturbances in uncontrolled diabetes and chronic pancreatitis

Age The disease is usually seen in childhood but may occur in adults A case was reported in a 41 year old man

Pathology

There are several anatomical features worthy of emphasis (1) the structure of the xanthomas ( ) the absence of a fatty liver (3) the lack of atheromatous changes in the blood vessels

The xanthomas are referred to as eruptive xanthomas and differ morphologically from the xanthoma tuberosum or planum They consist of inflammatory cells and very few fibroblasts Foam cells are very scarce and have to be searched for to be found The lipid deposits are primarily extracellular

The hepatic and splenic enlargement are not due to accumulation of fat No abnormal cells are found either in the liver or spleen and the fat content of the liver is not higher than in normal individuals Abnormal fat deposition does not involve the internal organs The basis of the enlargement of these organs is not clear on anatomical grounds

The blood vessels are likewise singularly free of atheromatous or fatty infiltration This is interesting in view of the normal blood cholesterol level in this disease

Clinical Features

Abdominal pain of a colicky type has been described in some cases The pain may be very severe and confined to the epigastrium or radiating to the entire abdomen The pain may be accompanied by nausea vomiting fever and distention suggesting an acute surgical emergency The pathogenesis of the pain is obscure

The eruptive xanthomas are very similar to the xanthoma diabeticorum and consist of small yellowish papules chiefly over the extensor surfaces of the extremities and over the buttocks but may occur on the scrotum lips and palate or all over the body They appear and disappear with variations in serum lipids A vesicular type of eruptive xanthoma has also been described which leaves an ulcerating surface upon rupture These lesions have been noted to increase during the summer

The spleen and liver are almost invariably enlarged in the childhood form of the disease These organs decrease in size with the decrease of serum lipids This is curious since fatty infiltration of the liver is not present In adults hepatosplenomegaly is not such a constant feature but the liver is occasionally enlarged The hepatic and splenic enlargement increase after the bouts of abdominal pain and fever Jaundice does not occur in this disease but has been described as the result of superimposed hepatitis

Ocular changes occur which are characteristic Lipemia retinalis consisting of cream colored veins and arteries nearly indistinguishable from each other occurs with hyperlipemias with a high neutral fat content The rarity of this finding and idiopathic hyperlipemia in general is demonstrated by the fact that only seven cases were reported in the literature up to 1950 (Dunphy) This observer also reported a case of lipid interstitial keratitis in a 41 year old patient with idiopathic hyperlipemia This appears to be a benign condition which cleared before the serum lipids were reduced

Signs suggesting endocrine disturbance have been described in one 16 year-old male by Harslof This consisted of adiposity sexual immaturity and dwarfism This patient also had hemorrhagic tendencies due to thrombocytopenia

Vascular disease such as atheromatosis of the coronary and other vessels seems to be uncommon in these individuals It is true that most of the reported cases are in young individuals and perhaps if they were followed to middle age the incidence of these vascular complications would be greater The high phospholipid cholesterol ratio seen in this disease may account for the lack of atherosclerosis

Etiology

The disease is due to a disproportion between the synthesis and excretion or destruction of cholesterol Since no impairment of excretion is involved it must be due to increased synthesis perhaps augmented by decreased destruction of this lipid The source of the cholesterol is endogenous and not exogenous Since the liver shows no anatomical or functional abnormalities it is difficult to implicate it in the production of this abnormality The skin is an important site of cholesterol synthesis and since it is the commonest site of its deposition one may surmise that the seat of the disturbance is in this organ Other organs especially the intestines testes and kidneys also synthesize cholesterol (Srere et al) The disturbed trait of cholesterol synthesis is inherited as an incomplete dominant characteristic (Wilkinson et al) There is no evidence that the increased cholesterol is exogenous or due to increased absorption

The localization of xanthomas depend on factors such as trauma surgery etc already discussed (page 443)

The condition is seen in both sexes and the age distribution is wide from the fourth to the eighth decade of life (34 to 80)

Clinical Features

Xanthelasma is the commonest of the skin lesions and occurs with slight or occasionally no elevation of the serum cholesterol The xanthoma tuberosum have similar distribution to those seen in biliary cirrhosis That this hereditary type of hypercholesteremia has no relation hip to biliary cirrhosis is indicated by the fact that no case of jaundice or biliary cirrhosis has been found in surveys of group with this hereditary characteristic (Adlersberg et al 1952 Wilkinson et al 1948) Liver enlargement is occasionally seen in these individuals but may be unrelated or just secondary to the metabolic disturbance Wilkinson and co workers found hepatic enlargement in 17% of their group Other findings include corneal arcus (senilis) which is common in some series and not in others but should be suspected as being due to hypercholesteremia

Cardiovascular abnormalities indicative of atherosclerosis are seen more frequently than in the general population These include hypertension angina pectoris myocardial infarction and electrocardiographic changes compatible with coronary artery disease This correlation between atherosclerosis and hereditary hypercholesteremia which is not dependent on dietary cholesterol suggests that dietary cholesterol may play no role in the non hereditary hypercholesteremia and other types of coronary artery disease

Laboratory Features

Hypercholesteremia must be present before an individual can be classified as belonging to this group xanthelasma however is not always present The hypercholesteremia is not as high as in biliary cirrhosis In Adlersberg s group the serum cholesterol ranged between 284 and 430 mg per 100 cc of blood with an average of 326 mg Cholesterol esters occur proportionately in the same amount as in normal individuals indicating no defect in esterification Thannhauser s cases showed similar concentration of cholesterol

The serum is not lipemic and phospholipid is the other lipid fraction increased and this is due chiefly to increased lecithin The phospholipid level is usually over 400 mg per 100 cc and therefore this fraction is increased even more than the cholesterol

The serum protein pattern in familial xanthomatosis shows a large β_1 globulin fraction which is apparently due to the increased lipid fraction since this electrophoretic peak is reduced by lipid extraction The β_1 fraction has a greater mobility than the same fraction in xanthomatous biliary cirrhosis The gamma globulin fraction which is markedly increased in biliary cirrhosis is normal in familial xanthomatosis (Lever and MacLean 1950)

Idiopathic Hyperlipemia with Eruptive Xanthomas (Buerger Grutz Disease)

This lipoid disturbance is characterized by increased neutral fats and hence lipemic serum as well as hepatosplenomegaly It is often referred to as lipidosis with hepatosplenomegaly or essential hyperlipemia with hepatosplenomegale lipoidose This disease was

endothelial proliferation and eosinophiles are the distinctive features of the lesions and separate them from the other xanthomatous lesions. Lesions in all stages of development may be found in any given patient. The phase of a given lesion depends not only on its chronological age but on the organ in which it is found. In acute and rapidly fatal cases only the hyperplastic proliferative reticuloendotheliosis is identified, and hence its possible relationship to Letterer-Siwe's disease.

Etiology

Nothing definite is known about the etiology. The liver cannot be accused of being primarily at fault. There is no evidence of a systemic disturbance of lipid metabolism. The proliferative and granulomatous nature of the early lesions suggested an infectious etiology, but this is likewise unsubstantiated. The disease seems to be a focal cellular alteration followed by a propensity of these cells for cholesterol.

Clinical Features

The clinical picture varies widely from the benign localized bone lesion of the adult to the serious systemic involvement of children. The disseminated form is seen in adults on occasion (Troxler and Niemetz).

The cutaneous xanthomas are of the disseminated variety and differ markedly from the xanthoma tuberosum and planum but may be confused with the eruptive xanthomas. The disseminated xanthomas may occur as an isolated feature or part of the visceral disease. The xanthomas have a predilection for the axillae, the neck and antecubital fossae. In later stages they may be scattered throughout the body. They consist of confluent pin-head-sized lesions forming lemon-colored patches. They later change to darker colors, becoming maroon, mahogany and dark brown in color. The deeper colors predominate in exposed areas like the neck. Lesions resembling petechiae may accompany xanthoma disseminata in children with the generalized form of the disease. These lesions are histologically endothelial proliferations around capillaries. The xanthoma disseminata show histologically proliferation of reticulum cells, fibrosis of tissue, eosinophilia and foam cells as described above. The cholesterol content of the involved skin is 10 to 20 times the normal value.

The xanthoma disseminata may also involve the eyelids while maintaining the same shape and structure. The disseminated xanthomas may become bulky and result in the tuberous form of xanthoma disseminata. The cutaneous xanthomas may be the sole localization of the eosinophilic granuloma or the skin lesion may be one manifestation of the systemic disease. The skin lesions cause no itching or discomfort and if attention is sought for them it is for cosmetic reasons. When skin lesions are found a search should be made for visceral lesions.

Isolated bone lesions may occur in the long bones, skull and pelvis or vertebrae. The upper part of the femur is a common site. These lesions may be asymptomatic and discovered on x-ray examination; if near joint they may cause pain on motion. Roentgenographic examination usually shows an osteolytic lesion; occasionally the lesion is diffuse and has a motheaten appearance. Occasionally there is an osteoblastic component. If no skin lesions are present the nature of the bone lesion has to be verified by histologic examination.

The classical triad of the disseminated form of the disease—Hand-Schuller-Christian disease—is exophthalmus, diabetes insipidus and bone defects in the skull. These manifestations are the result of the localization of the lesions in the skull, brain and dura mater. The invasion of the posterior pituitary results in the diabetes insipidus and large eosinophilic granulomas may push against the orbit producing exophthalmus and other deformities.

The majority of these cases occur under the age of 12 and most frequently in the third and fourth year of life (Nash and Cavanagh). The lesions may be widespread in the internal organs but produces no clinical symptoms calling attention to them. The organs involved include the liver, spleen, lymph nodes, lungs and thymus.

The involvement of the lungs is especially of interest because it may be confused with tuberculosis or other granulomas. Pleural involvement may produce pain. Spontaneous bilateral pneumothorax has been described in one adult patient with pulmonary eosinophilic granuloma (Troxler and Niemetz).

Laboratory Features

Liver function tests are normal. This is additional evidence that the abnormal lipid metabolism is not due to the usual type of liver disease but does not preclude a subtle disturbance confined to lipid metabolism.

Hyperlipemia with a milky serum is a diagnostic finding. In the absence of diabetes and serious pancreatic disease the presence of this type of hyperlipemia warrants a diagnosis of idiopathic hyperlipemia. The total blood lipids may reach nearly 10% (9 935 mg % Harslof) however the usual value is around 4 000 mg per 100 cc. The largest fraction is the neutral fat which is 2/3 or 3/4 of the total lipids. The phospholipids are slightly increased but proportionately more than the cholesterol. The free cholesterol may be more increased than the total cholesterol because the cholesterol ester are usually relatively decreased. The ratio between the phospholipid and total or free cholesterol is higher than normal.

Hyperglycemia and glycosuria have been observed in some of the adult patients with hyperlipemia. The lipid disturbance of these patients has to be considered as idiopathic and not secondary to diabetes for the secondary hyperlipemia of diabetes occurs only in severe uncontrolled diabetics with acidosis while the carbohydrate abnormality in the adult idiopathic hyperlipemia is very mild and easily controlled. It can only be surmised that this lipid metabolic abnormality in the adult is also accompanied by a carbohydrate disturbance.

Treatment

Low fat diets maintained over prolonged periods of time (several months) result in a reduction of the hyperlipemia but the serum usually remains lipemic and the neutral fat does not return to a completely normal value. With the reduction of the plasma lipids the liver and spleen decrease in size and the eruptive xanthomas disappear. The use of lipotropic substances such as choline methionine and inositol appear to be of no value.

Eosinophilic Xanthomatous Granulomas

Eosinophilic xanthomatous granuloma also known as the Hand Schüller Christian disease or the Schüller Christian disease or syndrome or simply as eosinophilic granuloma belongs to *the group of normocholesteremic xanthomatoses*. This disease entity is of interest here because of the disseminated type of skin xanthomata which may be confused with other xanthomas and because of the possible secondary involvement of the liver.

Pathology

The disease can be conveniently divided into the disseminated visceral eosinophilic granulomas with brain involvement and diabetes insipidus usually occurring in childhood and the isolated eosinophilic granuloma of bone commonly seen in adults. In spite of this marked difference in extent of organs involved it is probably the same disease process.

The organs involved in the diffuse process are the skin skeletal system central nervous system lung pleura pericardium lymph nodes spleen and liver. The *predominant localization determines the* clinical syndrome.

The solitary bone lesions were thought by Lichtenstein and Jaffe to be unrelated to the diffuse form and an independent disease. However other workers have amply demonstrated that the isolated bone eosinophilic granulomas are but one manifestation of the same systemic disease (Fraser 1935 Farber 1941 1944).

Histologically the individual lesions show variations according to their stage of development. There are three phases recognized in the development of the mature xanthomatous lesion as follows (1) hyperplastic proliferative phase (2) granulomatous phase and (3) xanthomatous phase.

In the hyperplastic proliferative phase some of the capillary endothelial cells become swollen and detached from the vessel wall and migrate to adjacent tissue spaces. Some lipoid accumulation in the cytoplasm of reticulum cells takes place and the area is *infiltrated with eosinophiles*.

In the granulomatous phase the capillaries lose their structural identity and are replaced by oval or fusiform cells. New capillaries proliferate and scattered among the eosinophiles and the reticulum cells are giant cells of small nuclear type known as Touton cells.

In the xanthomatous phase *the reticulum* cells become distended and foamy from the increased lipid content evolving the "foam" cells. The mature foam cells lie at the periphery of the lesion and the smaller and younger cells lie at the center of the lesion.

These lesions advance to senility with the formation of the fibrous phase when connective *replacement* of the foam cells takes place. The lesion now shows chiefly fibroblasts with few foam cells and extracellular lipid deposit. The presence of reticulo-

and spleen are marked. The liver is larger in this disease than in Gaucher's disease. Lymph node enlargement is also present. The diffuse brownish pigmentation of the skin and bluish black spots of the mucous membrane of the mouth and mental deterioration are characteristic findings.

The liver is markedly enlarged and grossly resembles a fatty liver. Microscopically, the foam cells are seen to fill the sinusoids, and the entire architecture is so disturbed as to defy recognition. Periportal connective tissue is less marked than in Gaucher's disease. Thannhauser cites two adult cases with cirrhotic changes in the liver.

In spite of the tremendous involvement of the liver, the liver function tests remain normal in most instances.

77

Treatment of Cirrhosis, Diffuse Liver Disease, and Liver Failure

Prophylactic

Chronic liver disease, like many other chronic diseases, has a tendency to progress and become irreversible. The aim of the clinician should be, therefore, to prevent acute liver injury, and when it does occur, to forestall chronicity. Toward this end it is well to recall the groups of etiologic factors which have demonstrable injurious effect on the liver. These etiologic factors, which were discussed in the appropriate sections, are:

1. Toxins (section V, p. 15[illegible])
2. Infectious agents (section VI, p. 180)
3. Circulatory disturbances (section VIII, p. 321)
4. Dietary deficiency (section VII, p. [illegible]85)
5. Obstruction to outflow of bile (section IX, p. 431)

These various etiologic factors produce under controlled laboratory conditions or occasionally in a clinical setting specific types of injury. As a rule, in the advanced case of cirrhosis or chronic liver damage several or all of these factors have played a varying role in the resultant disease.

General Therapy

Rest

Bed rest is one of the oldest, simplest, and most effective of therapeutic agents. In acute diseases of the liver it must be rigidly enforced until complete recovery occurs. This may require several months of rest. In cirrhosis, which is a chronic disease and its duration is measured in years rather than months, complete bed rest throughout its course is neither possible nor desirable. During the inactive, latent, or compensated phase of the disease, only slight or moderate reduction in activity is necessary. The degree of curtailment of activity must be individualized and depends upon the patient's reactions, such as fatigability, weakness, etc.

In active cirrhosis, the criteria of which were pointed out on page 390, bed rest must be enforced. Bathroom privileges may be allowed. Bed rest should be continued until signs of activity have subsided. Chief among these signs are fever and jaundice. Although ascites is included among the signs of active (decompensated) disease, because it may continue for years, bed rest throughout its presence may be impracticable. I have seen patients with ascites

Laboratory Features

Blood lipids The most important laboratory finding in this disease is a negative one All the serum lipids including the cholesterol are within the normal range hence the classification normocholesteremic xanthomatosis

Liver function tests These tests may be normal even when the liver is involved However when this organ is considerably involved the alkaline phosphatase may become elevated the bromsulphalein test may show abnormal dye retention and some of the flocculation tests may be mildly abnormal

Liver biopsy When the liver is extensively involved needle liver biopsy may establish the diagnosis Histologic diagnosis of eosinophilic granuloma by liver biopsy has never been made to my knowledge This approach should be kept in mind when a more accessible lesion is not available for biopsy The liver granuloma frequently fails to show eosinophilic aggregates

X ray The lesions involving the skeleton are most readily demonstrated by roentgenography As has been stated before (p 571) the bone changes are usually osteoclastic The skull may show large bony defects Osteoblastic changes may result in sclerosis of the involved area or a mottled appearance The diagnosis cannot be established from the x ray alone and the suspicion must be verified by biopsy and histologic examination

Treatment

The localized bone granuloma is responsive to irradiation therapy and if accessible can be removed surgically The generalized visceral disease does not respond to any form of specific therapy and can only be treated symptomatically

Gaucher s Disease

This disease is also called reticular and histiocytic cerebrosidosis Gaucher s type of lipoid cell hepatosplenomegaly

Gaucher s disease is not primarily a disease of the liver but this organ can be involved Because of this it becomes necessary to consider this rare disease as a possible cause for hepatomegaly

This disease is a familial disorder involving a derangement of lipid metabolism in which cerebrosides accumulate in abnormal amounts in histiocytes of the reticuloendothelial system These cerebroside laden histiocytes involve the spleen and bone marrow chiefly but also the lymph nodes and liver

It is predominately a disease of childhood but an adult form has been described

The splenic enlargement overshadows the hepatic enlargement but the liver may be considerably enlarged The bone marrow involvement results in skeletal pain and x ray changes and hemorrhagic tendencies due to thrombocytopenia The lymph node enlargement may be detected clinically Another characteristic is the patchy pigmentation of the skin and wedge shaped thickening and pigmentation of the conjunctivae

The involvement of the liver may result in gross changes simulating portal cirrhosis Microscopically increased fibrous tissue has been described (Teilum) The characteristic Gaucher s cells are found in the center of the lobule Hemosiderosis of the liver as well as of the other organs occurs

Liver function tests may become abnormal when this organ is markedly involved Needle biopsy of the liver may reveal the characteristic cells and determine the diagnosis however biopsy of the spleen or bone marrow is more likely to yield the characteristic morphological features

Niemann Pick s Disease

This disease is also known as reticular and histiocytic sphingomyelinosis Niemann Pick type lipoid cell splenohepatomegaly essential lipoid histiocytosis

This disease is also a rare familial congenital disorder of lipoid metabolism It differs from Gaucher s disease by the accumulation of sphingomyelin in the cells and the involvement of any organ including mucous membranes and not just the reticuloendothelial system

The disease is almost exclusively one of infants and children and only very rarely is it seen in an adult The enlargement of the liver

and spleen are marked The liver is larger in this disease than in Gaucher's disease Lymph node enlargement is also present The diffuse brownish pigmentation of the skin and bluish black spots of the mucous membrane of the mouth and mental deterioration are characteristic findings

The liver is markedly enlarged and grossly resembles a fatty liver Microscopically the foam cells are seen to fill the sinusoids and the entire architecture is so disturbed as to defy recognition Periportal connective tissue is less marked than in Gaucher's disease Thannhauser cites two adult cases with cirrhotic changes in the liver

In spite of the tremendous involvement of the liver the liver function tests remain normal in most instances

77 — Treatment of Cirrhosis, Diffuse Liver Disease, and Liver Failure

Prophylactic

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1 Toxins (section V p 15)
  Infectious agent (section VI p 180)
3 Circulatory disturbances (section VIII p 3 1)
4 Dietary deficiency (section VII p 285)
5 Obstruction to outflow of bile (section IX p 431)

These various etiologic factors produce under controlled laboratory conditions or occasionally in a clinical setting specific types of injury As a rule in the advanced case of cirrhosis or chronic liver damage several or all of these factors have played a varying role in the resultant disease

General Therapy

Rest

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respond to ambulatory treatment Bed rest has been prescribed on an empirical basis There is evidence however that exercise increases the metabolic demands on the liver and circulatory changes deleterious to the liver occur on merely assuming the upright position (Culbertson et al 1951)

Alcohol

Interdiction of alcohol is usually advised in liver disease especially in portal cirrhosis with an alcoholic history The role of alcohol in the production of liver damage has not been established This problem has been discussed on pages 295–369 Reduction of the alcoholic intake is unquestionably important to obviate interference with the diet Small amounts of alcohol may not be injurious if the diet is adequate Withdrawal of alcohol may at most play only an accessory role (Phillips et al 1952)

Diet

There is no dispute that an adequate diet is essential in the treatment of liver disease There are some differences of opinion as to what constitutes an adequate diet The importance of the protein requirements of the liver has been discussed in Section VII page 289 The necessity of an adequate amount of protein essential amino acids and especially the sulfur amino acids is clear from laboratory as well as clinical observations The revival of the idea that excessive protein intake may be *deleterious in severe liver disease (p 412)* should not be taken too seriously since it is usually difficult to maintain an adequate food intake in advanced liver disease The negative nitrogen balance in liver disease can be combatted only by increasing the protein intake

Carbohydrates must be included in sufficient amounts as a quick source of energy and also in order to spare the needed proteins Fats should not be administered in excessive *amounts in portal cirrhosis (fatty cirrhosis)* or fatty livers Experimental evidence of the deleterious effects of fats has been recounted (p 285) One of the sources of fat for a fatty liver is exogenous therefore it seems illogical to administer more of this substance The steatorrhea of liver disease is an additional argument for reduction of dietary fat More over excessive amounts of fat in the diet may not be well tolerated and result in dyspepsia The fat content should be adequate for palatability

The diet should therefore contain 150 gm of proteins and 400 gm of carbohydrates and less than 100 gm of fat This formula need not be adhered to rigidly and should be fitted to the particular patient s caloric needs (size of patient) and dietary idiosyncrasies The caloric intake is so important that the skill of the individual preparing the food is an important factor in the therapeutic machinery The protein content of the diet may be attained by high protein between meal beverages (Table 75)

Parenteral Foodstuffs

If the patient is so ill or has so severe an anorexia that his oral intake *is insufficient to* meet the above requirements carbohydrates and proteins may have to be administered intravenously Glucose can be given in 10 per cent solution in distilled water Because of the route of administration and the higher blood sugars attained it is possible to stimulate a damaged liver to greater glycogen storage (Soskin et al) If given sufficiently slowly little of the glucose is lost in the urine The administration of insulin may defeat the therapeutic aim by stimulating glycogen storage in the muscle and thus divert *it from the* liver

Protein requirements can be met to a certain extent by intravenous administration of amino acids as protein hydrolysate It is known that

TABLE 75

Formula for Liquid Feedings in Cirrhosis

	P t	*Fat*	*C bo- hyd t s*
1 quart (1000 cc) skimmed milk	3 gm	4 gm	48 gm
1 cup (8 oz—240 gm) skimmed milk powder	43	1	62
4 eggs	24	0	
Dextrose 4 oz (120 gm) (or sucrose)			1 0
Vanilla for flavor			
Totals	99 gm	25 gm	230 gm
Total Calories 1545			

the liver deaminizes amino acids and synthesizes proteins from them; these functions may be lost in severe hepatic necrosis (Dunn et al., 1950). In spite of these facts, it has been demonstrated that the cirrhotic liver can utilize amino acids (Eckhardt et al., 1948; Lewis et al., 1947; Ross and Elman, 1948; Terry et al., 1948 and Whipple, 1948). The more completely hydrolyzed hydrolysates can be used more adequately than the ones containing polypeptides (Cannon, 1949; Smyth et al., 1948). Although as high a concentration as 15 per cent (Altshuler et al.) has been administered experimentally, in practice 5 per cent protein hydrolysate in 10 per cent glucose is preferable. Amino acids should be administered slowly because of the possible production of nausea. The use of normal saline is avoided because of possible sodium retention. It is desirable to administer these solutions after meals because they interfere with oral intake of food by decreasing the appetite and by hampering the use of an arm. The time element makes it difficult to administer more than 1,000 cc. between meals, that is, in an appropriate period of four hours, so that if more fluids are administered they inevitably interfere with the oral feedings. It cannot be overemphasized that the most satisfactory way of meeting the nutritional requirement in health as well as disease is the oral route. Neither the caloric requirements (only about 1,500 cal. in 3,000 cc. of 10 per cent glucose with 5 per cent amino acid) nor the requirements for minerals, vitamins, etc., can be adequately met by the parenteral route.

Plasma can be used parenterally to add to the protein need. This is of particular aid when the plasma proteins are very low. The use of albumin will be discussed later in the treatment of ascites. One should use irradiated plasma to avoid, if possible, the introduction of the hepatotoxic virus (S.H. virus). Plasma is probably not used as efficiently for tissue protein needs as amino acids. The whole proteins have to be broken down to their constituent amino acids before they are used as fuel or resynthesized into tissue proteins (Cannon, 1949; Eckhardt et al., 1948; Terry et al., 1948).

Vitamin Supplements

Vitamin supplements should be administered for the following reasons: they may not be absorbed in normal fashion from foods; there may be a disturbance in their utilization; or they may be required to counteract the noxious process in the liver or aid in its regeneration. The role of the B complex in hepatic injury has been discussed (p. [illegible]9). These vitamins may be administered by mouth in the form of powdered yeast, [illegible] oz. (60 gm.) daily. This can be mixed with the high protein beverages, but if not tolerated well, it can be administered as a B complex concentrate. B complex can also be administered intramuscularly. Some of these products have vitamin C incorporated into the ampules of B complex (Berrocca—C, Roche; Betalin Complex, Lilly). Ascorbic acid can be given by mouth, 400 mg. a day. In patients in hepatic coma, parenteral administration becomes necessary. This will be discussed later.

Vitamin E may be useful in the treatment of postnecrotic cirrhosis in accordance with information obtained from animal experiments (p. 92). Alpha tocopherol should be administered in doses of [illegible]00–300 mg. daily. Vitamin A may not be stored or absorbed properly, and hence additional Vitamin A, 50,000 to 100,000 cc., can be given daily. If fat absorption is poor, it should be administered parenterally. For the use of Vitamin K, see page 578. Cod liver oil, probably because of its fatty acid content, may be injurious to the liver of some animals. The need of Vitamin D in cirrhosis is questionable and, if indicated, can be administered in the form of viosterol.

Lipotropic agents

The role of deficiency of lipotropic agents in experimental cirrhosis and the rationale of its use in cirrhosis in man has been discussed (pp. [illegible]85 and 311). Some observers indicate that the lipotropic factors are helpful even when added to an adequate diet (Beams, 1946 and 1947; Broun and Muether, 194[illegible]; Steigman, 1948), while others contend that it has no merits when an adequate diet is taken (Jones and Volwiler, 1947). Undoubtedly these agents would be most effective in fatty liver and fatty

cirrhosis (large livers) and in individuals whose protein intake is limited

Methionine is administered in 0 5 gm tablets three to six grams a day in divided doses Choline can be administered as tablets or in liquid form as syrup of choline dihydrogen citrate 25% solution The dose is three to six grams a day Choline occasionally causes diarrhea The reader should refer to page 311 where the question of the absorbability of choline from the intestinal tract is discussed

Lipotropic properties have been attributed to inositol (McHenry) but its efficacy in liver disease has not been established There are preparations which contain a combination of choline methionine and inositol In this combined form the methionine and choline is present in insufficient amounts [(Methiscol (U S vitamin) 9 capsules = choline 2 5 gm methionine 1 gm inositol 0 75 gm)] Cystine in combination with choline has a lipotropic effect All the lipotropic substances should be administered after meals to avoid any anorexic effect

Liver extract in its crude form has been used for many years empirically in the treatment of liver disease Later it has been thought to be of value because of its richness in the entire B complex More recently a special preparation of liver extract has been recommended for intravenous use (Intraheptol Labby et al 1947) Finally B_{12} has been found to have a lipotropic effect and have some protective effect against carbon tetrachloride poisoning in animals (Drill and McCormick 1949 Gyorgy 1950 Koch Weser et al 1950 Mushett 1950) The probability is thus evolved that the value of liver extract in the treatment of liver disease depends on its B_1 content or some as yet unknown fraction and if so it may be more efficacious in its purified (15 u/cc) than in its crude form (Clark)

The intravenous form of liver extract therapy (intraheptol) has not appeared to me to be more effective than the old extracts for intramuscular use I have noticed nausea anorexia and slight rise of temperature even when intraheptol was used with great caution Therefore I prefer the intramuscular route Two to three cubic centimeters of the crude or purified liver extract can be administered intramuscularly every other day and B_1 60 micrograms intramuscularly every day One must emphasize that these agents are not used for their hematopoietic effect

Hormones

Testosterone seems to be indicated in the treatment of cirrhosis in view of the feminizing features noted in advanced liver disease (p 407) The known protein sparing effect of testosterone (Kenyon et al and Wilkins et al) and the negative nitrogen balance observed in liver disease (Cook and Van Auken) add to the rationale of testosterone medication The sodium retaining properties of this hormone may produce an unfavorable reaction however Rosenak and his associates used it in six cirrhotics with ascites and edema and noted no evidence of increased water and sodium retention It has been used as testosterone propionate in oil 25 to 100 mg intramuscularly three times weekly Methyl testosterone 25 mg sublingually daily may be used instead of the parenteral product This hormone may have a very favorable effect on the pruritus of jaundice (Lloyd Thomas and Sherlock)

The use of cortisone and the adrenocorticotropic hormone has been discussed in several places in this book (pp 283 and 474) Its stimulating effect in general and on the appetite in particular has unquestionable merit This may be especially helpful in hepatic coma which will be discussed later (p 577) The use of these hormones must be guarded in the presence of ascites and edema because of their sodium and water retaining effects Acceleration of development of ascites and edema and decreased sodium excretion has been noted during the use of these hormones (Blahd et al 195 Kark et al 1951) After discontinuance of these hormones marked diuresis may occur which can clear the ascites and edema More recently Kark and his group noted no deleterious effect from these hormones when sodium restriction was meticulously enforced (Chapman et al 1952)

Hypercoagulability of the blood was noted as a side effect in some patients with liver disease treated with ACTH (Eisenmenger et al

195) This occurs in spite of continued hypoprothrombinemia. Plasma antithrombin activity was subnormal and was not elevated by the hormone therapy. While this is advantageous in patients with marked bleeding tendency, it exposed patients to thrombotic phenomena. Portal vein thrombosis was noted by Eisenmenger and his associates in three patients with cirrhosis, and I have seen it in one patient with cirrhosis treated with ACTH.

The dosage and mode of administration will be discussed under treatment of hepatic coma. In general, these hormones find their greatest usefulness in hepatic coma. In other stages of cirrhosis they should be used only when other forms of therapy are ineffective, when anorexia is marked, and when the downhill course remains unchecked.

Treatment of Troublesome Symptoms

Hepatic Coma

Central nervous system symptoms developing abruptly in diffuse liver disease is a signal of the approach of dreadful hepatic coma. Insomnia and restlessness are particularly important since the use of barbiturates and opiates may push the patient over into coma and death. Such tragic results are all too common when an enthusiastic but poorly informed house physician administers a potent dose of barbiturate to a restless patient with cirrhosis. The damaged liver is unable to detoxify these substances, and hence they should not be used in severe liver disease. An occasional dose of barbital, which is excreted by the kidneys, may be tried. Potassium bromide is a safe sedative. Paraldehyde and chloral hydrate may also be used in small doses even though they may have some hepatotoxic effect. Sometimes scopolamine alone may allay restlessness.

Hepatic coma and precoma should be treated vigorously, for although the prognosis is very grave, an occasional patient can be rescued from coma. Because of the extreme anorexia, drowsiness, and the final loss of consciousness, therapy must be either parenteral or by stomach tube, or both.

Fluid balance can be maintained by intravenous fluids. The output and intake of fluid must be carefully balanced in order not to overburden the circulation and increase edema and ascites. 10% glucose in distilled water can be given up to 3000 cc. per day. To this should be added the potent vitamin cocktail: 500 mg. ascorbic acid, 100 mg. thiamine chloride, 500 mg. niacine and 50 mg. of riboflavin in each flask of fluid. Vitamin B_{12} mentioned before may be helpful in hepatic coma; 60 micrograms daily intramuscularly should be adequate, although much larger doses have been advised.

Sodium chloride should be avoided if ascites and edema are present. Its excessive use may precipitate these complications; however, the serum chloride and sodium may be low, and hence sodium chloride may have to be given. If acidosis is present and the hyponatremia is accompanied by a normal chloride level, sodium lactate can be administered as the 1/6 molar solution. Administration of sodium should be accompanied by chemical determinations of the blood to avoid over treatment.

Other electrolytes may also have to be administered because their serum levels are low. Foremost among these are potassium, calcium and phosphorus. Potassium chloride may be added to the intravenous fluid (1 or 2 gm./1000 cc. of fluid). Calcium can be given in a similar manner as the gluconate or lactate.

Liquid feedings administered by stomach tube can more adequately maintain nutrition if the patient remains comatose for a considerable period of time. Frequently liver failure is preceded or accompanied by hemorrhage from esophageal varices. Intragastric feedings can be administered through the gastric tube of the esophageal tampon (Figure 67, page 553).

A useful formula for tube feedings is outlined in Table 75.

This mixture can be modified in various ways. The carbohydrate can be increased by adding more dextrose. The protein can be decreased or increased by changing the amount of skimmed milk powder. The calories and fat can be raised by increasing the eggs or adding cream. The salt content can be decreased by replacing the milk powder with one of the commercial protein concentrates, such as Lonalac (Mead Johnson), delco granules (Sharp and Dohme), melactine (Squibb), protinal (National Drug Co.), Brewer's yeast powder and

other vitamins may be added to it This liquid mixture contains not only adequate calories proteins and carbohydrates but contains a good mineral mixture potassium calcium and phosphorus Two quarts of this mixture yields over 3000 calories This mixture can be made quite palatable by varying and adjusting the flavoring agent so that it can be used as a supplementary between meal feeding

Antibiotics have a dual usefulness in hepatic coma Pulmonary and other infections may be prevented by antibiotics and of course antibiotics can be used when infections become evident In such cases the drug suitable for the particular infection should be used Aureomycin and terramycin have been advocated in hepatic coma and hepatic failure because their sterilizing effect on the intestinal contents may decrease the endogenous toxins entering the liver Since both of these antibiotics are excreted into the intestine with the bile they effect the intestinal flora even when administered intravenously Oral administration has a disadvantage because of the occasional production of nausea and vomiting Aureomycin and terramycin also can be administered in 1 gram dose per day orally divided into four doses and intravenously 500 mg diluted in a liter of fluid once or twice a day

Corticotropin (ACTH) and cortisone have been advised along with the antibiotics and these newer therapeutic agents are thought to offer patients with hepatic coma a greater chance for recovery ACTH is preferable to cortisone ACTH can be administered intravenously 10 to 20 units per 24 hours When the serum sodium is low, the higher dose may be used and the sodium retaining effect of the hormone would actually be helpful If the serum sodium is normal and there are ascites and edema the smaller dose should be used along with sodium restriction Potassium chloride should be administered intravenously or orally when ACTH is given The oral dose of potassium salts is 4 to 10 gm a day in divided doses The intramuscular dose of ACTH is 80 to 100 units divided into four equal doses or in a single dose if the gel is used

Cortisone should be given intramuscularly 50 mg every 12 hours The oral administration may be unreliable because of possible absorptive impairment Plasma and especially salt free albumin is useful in the treatment of hepatic coma Its use is discussed in detail on page 579

Hemorrhagic Tendency

The tendency to hemorrhage from sources other than esophageal varices can be a troublesome and dangerous complication of severe liver disease Spontaneous hypoprothrombinemia may become severe and does not respond to synthetic vitamin K (menadione) administration It is possible that the natural vitamin K may be more effective (Quick and Collentine 1951 Strangell 1952) Vitamin K should be administered prophylactically when antibiotics are used for these impair intestinal synthesis of vitamin K This vitamin should be administered in 20 mg doses daily excessive doses may produce a paradoxical effect and lower the prothrombin level of the blood (Unger and Shapiro) (p 32)

Increased coagulability of blood from ACTH therapy has been mentioned (Eisenmenger et al) Gingival bleeding has subsided with the use of this drug Blood transfusions are of help in the hemorrhagic phenomena For treatment of esophageal varices see Chapter 50 page 355

Anemia and Anoxia

The anemia of liver disease does not respond to iron therapy unless the anemia is due to blood loss Blood transfusions may be required to halt the deleterious effects of anoxia on the liver Oxygen may be helpful if the anoxia is due to causes other than anemia

Pruritus

The pruritus of jaundice is most commonly experienced in post hepatic rather than hepatic jaundice Pruritus may become a troublesome symptom Methyl testosterone orally or intramuscularly may produce relief ACTH and cortisone may also relieve the itching of jaundice Corticotropin and cortisone lower the plasma bile salts and this may be their mode of action in relieving pruritus Benadryl hydrochloride (diphenhydramine hydrochloride) in 50 or 100 mg doses may result in symptomatic

relief of pruritus Procaine hydrochloride o cc of the 1 % solution diluted in 1000 cc of dextrose in water al o produces temporary relief The enzyme adenosine triphosphate has been recommended by Pelner and Waldman They used 20 mg intramuscularly three times a day Ergotamine tartrate orally or parenterally has been used for the pruritus of jaundice It is not an innocuous drug for repeated use and ha not been effective in my experience Local applications of antipruritic ointment sodium bicarbonate and oatmeal baths may give temporary relief

Treatment of Hepatorenal Syndrome

(See Chapter 65 page 484)

Treatment of Ascites and Edema

The factors involved in the production of ascites have been discus ed (p 396)

From the therapeutic point of view the two factors involved in ascites and edema formation that are most susceptible to correction are the hypoalbuminemia and the sodium retention

Salt Poor Human Albumin

When the oral administration of proteins is ineffective in raising the serum proteins administration of whole proteins in the form of plasma or better as human serum albumin is advisable The concentrated salt free serum albumin is advised Favorable results on edema ascites and even liver function tests and hepatic coma have been reported (Armstrong 1948 Faloon et al 1949 Kark et al 1951 Kunkel et al 1948 Post et al 1951 Thorn et al 1946) from it Kark and co workers claim that in addition to the favorable effect on the plasma osmotic pressure the increased protein tored in the cells of the capillaries forms an o motic barrier against fluid salt and protein leakage Post and co workers advised the use of one unit 25 gm per 100 cc first day increased to 50 gm a day thereafter While diuresis may occur the first week 600–700 gm may be required for significant effect If no results a e obtained from this amount of albumin the ca e may be judged nonresponsive to this form of therapy Armstrong has uggested removing the ascitic fluid completely and following this by injection of albumin

The disadvantages of serum albumin therapy are three fold (1) It does not always rid the patient of ascites even though it raises the plasma albumin and o motic pres ure (Faloon et al 1949 Mankin and Lowell 1948 Patek et al 1948) (2) it may produce serious complications such as pulmonary edema (Watson and Greenberg 1949) and precipitate bleeding from esophageal varices and (3) it is very expensive

Sodium Restriction

The disturbed liver endocrine renal axis produces edema and a cites by retaining salt and water Restriction of dietary sodium seems to rectify the disturbed physiology with resultant diure is (Kark et al 1951 Eisenmenger 1952) For this reason diets containing 200 to 500 mg of sodium (equivalent to 0 5 to 1 25 gm of NaCl) should be prescribed The greater salt restriction may be difficult to follow and therefore the patient should be tried on the more liberal (1 25 gm NaCl) diet and if diuresis does not occur greater restriction may have to be resorted to In either case the commercial sodium poor proteins may have to be used a well as sodium poor bread and other special foods One of the sodium free alt ubstitutes on the market such as neocurtasal (Winthrop Stearns) co salt (Funk) can be used Low salt foods and sample menus are given in Tables 76 and 77

The alt restriction may be relaxed after adequate diuresis and disappearance of the excessive accumulations of water Patients *with severe liver disease should be cautioned* against excessive salt intake at all times The optimum restrictions in re pect to salt must be individualized

Cation Exchange Resins

Cation exchange resins * which remove sodium from the gastrointestinal tract and prevent its absorption can be used in conjunction with a more liberal intake of sodium (over 3 gm NaCl daily) These consist of an acid resin and potassium resin The first to reduce the dangers of acidosis and the second to reduce the

Ca b R n Lilly

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Table 76
Low Sodium Foods

Fresh vegetables are low in sodium except the following
- Beets
- Celery
- Spinach
- Sauerkraut

Fresh fruits and frozen fruits are low in sodium and may be eaten

Beverages

Coffee	Apple juice
Cocoa	Lemonade
Tea	Orange juice
Postum	Pineapple juice
Coca-cola	Grape juice
Ginger ale	*Grapefruit juice*

Desserts—made with Lonalac sugar honey fruits and plain gelatin

Caraway	Nutmeg
Cinnamon	Paprika
Curry	Pepper various types
Garlic	Vanilla extract
Ginger	Vinegar
Mustard powder	Salt substitutes

No sal is to be added in preparation of food *Do not use* salted crackers salted or smoked meats pickled fish *olives pickles potato ch ps salted nuts onion or garlic* salt catsup Worcestershire sauce

Cereals

Corn meal	Rice puffed and cooked
Farina	Tapioca
Instant Ralston	Wheat puffed and shredded
Oatmeal	Wheatina

Bread—Low sodium bread purchased or prepared

Spreads
- Butter unsalted
- Honey
- Jelly
- Jam
- Marmalade

chances of hypokalemia Ammonium resins have been used but *it has been suggested that* these may result in a rise of blood ammonia and precipitate hepatic coma (Gabuzda et al) Forty to sixty grams (4 tablespoons) of the resin is administered in divided doses in water fruit juice or sprinkled on cereals If given in water or fruit juice it should be administered between meals to avoid possible anorexic effects

Cation exchange resins are not entirely innocuous They may produce acidosis and hence the CO combining power of the blood should be watched Other ions besides sodium are extracted hence hypocalcemia should be guarded against Calcium as well as potassium salts may have to be administered to curtail their loss The electrolyte disturbance is especially serious when liver failure is marked

Table 77
Sample of Low Salt High Protein, High Carbohydrate Diet

	Weight gm	Protein gm	Fat gm	Carbohydrates g
Breakfast				
Orange juice or other fruit juice mentioned above	100	6		10 0
Oatmeal or other cereal	150	4	3	0 4
Eggs	2	12 0	12 0	
Butter	10		8 0	
Milk skimmed	100	3 5	0 4	4 8
Water	100			
Lonalac	50	13 5	14 0	19 0
Bread salt free (3 slices)	60	6 0	8	3 0
Jelly	30			18 0
Total Grams		39 8	37 5	104
Lunch				
Beef lean salt free or veal	150	6 0	0 0	
Potatoes salt free	100	0		20 0
Vegetables (may be incorporated in soups)	00	0		10 0
Bread salt free	60	6 0	0 8	3 0
Jelly—marmalade etc.	30			18 0
Milk skimmed	100	3 5	0 4	4 8
Lonalac—add cocoa etc. or chocolate	50	13 5	14 0	19 0
Fruits—*apple pears etc* cooked or raw (sugar may be added)	100			10
Total Grams		53 0	35	113 8
Supper				
Egg (1)		6 0	6 0	
Cottage cheese (salt free)	150	30 0	1 5	6 0
Potato salt free	100	0		20 0
Vegetabl s	00	0		10 0
Bread salt free	60	6 0	0 8	32 0
Butter (1 pat)	10		8 0	
Jelly (marmalade etc)	50			32 0
Gelatin (not ready made)	100	1		19 4
Milk skimmed	100	3 5	0 4	4 8
Water	100			
Lon lac	50	13 5	14 0	19 0
Total		64	30 7	143 2
Grand Totals		157 0	103 4	361 2

Drastic depletion of the body sodium may result in the serious salt depletion syndrome (Schroeder). This is especially likely to occur when paracentesis and diuretics are used in conjunction with the resins.

Diuretics

Excretion of salt and water may be stimulated by means of diuretics. Ammonium chloride may be used alone but its effect is usually slight. In gravely ill patients it may result in an increase in blood ammonia and precipitate coma (Gabuzda et al.). However, I have used it for prolonged periods of time without any noticeable untoward effect. The dose is 1.0 gm four times a day in enteric coated or uncoated tablets. The uncoated tablets are more effective but produce digestive disturbances.

I am opposed to mercurial diuretics in patients with liver disease because of the possible deleterious effect of even small doses of mercury on an already damaged liver. Moreover, as was pointed out by Hilton in a recent study of the problem, mercurial diuretics alone may not produce an appreciable increase in sodium excretion and a negligible decrease in accumulated fluid. Oral administration of ammonium chloride during the period of mercuhydrin (methoxyoximercuripropylsuccinylurea) administration caused a marked increase of water and sodium excretion. Chloride and potassium excretion is greater than sodium excretion during the basal period and their increase during diuresis is more marked. As much as 250 m Eq of potassium is excreted in 24 hours during mercurial diuresis (Hilton). One has to watch for hypokalemia which may result in a clinical picture similar to hyponatremia.

Mercuhydrin can be administered intramuscularly in 1 or 2 cc doses two or three times a week. Mercurial diuretics should be resorted to after the more innocuous forms of therapy have failed.

Surgical Treatment of Ascites

Paracentesis. If the abdomen is markedly distended with fluid to the point that it produces pain and interferes with respiration, removal of fluid by paracentesis becomes necessary. Paracentesis should be done as infrequently as is compatible with the comfort of the patient. Removal of the ascitic fluid by mechanical means results in further loss of albumin and prompt reaccumulation of fluid unless the other measures described above are carried out simultaneously.

Paracentesis can be done by a trochar after anesthetizing the area with 1% procaine. The bladder should be emptied. The procedure can be done with the patient sitting in a chair. In this position the site of insertion of the trochar is as near the pubis as is technically possible and either to the right or left of the midline. The skin and subcutaneous tissues are nicked with a pointed scalpel and the trochar inserted.

The procedure can be carried out with the patient in the recumbent position. In this position the trochar is inserted in either flank in the most dependent position over an area of maximum dullness. When the stylet of the trochar is removed the fluid flows freely. The fluid should be removed slowly to avoid an untoward reaction from sudden decompression. In paracentesis done in the ascites of cirrhosis no serious complications should be encountered. Injury of the intestines should not occur if paracentesis is done over an area of dullness and the trochar is handled gently. One should not insert the trochar in an area of dilated veins. I have not seen any serious complications in paracentesis carried out with the above technique. Fluid may continue to drain from the wound for several days.

Bronfin and associates proposed the insertion of a vinyl tubing into the peritoneum through a 14 gauge needle for drainage of ascitic fluid. The plastic tube is left in the peritoneal cavity for 8 to [illegible] hours. They regard this as a safer procedure than the trochar method.

Other surgical procedures. Many of the surgical procedures used for relief of portal hypertension (p. 355) have also been recommended for the treatment of ascites. The shunt procedures are usually unsuccessful in relieving ascites and most patients with ascites are too ill to withstand a portacaval shunt.

Various surgical procedures have been proposed for diverting the ascitic fluid into the circulation. One of these procedures consists of implanting a button like device subcutaneously

which facilitates drainage of the ascitic fluid into the subcutaneous tissues where it is absorbed into the general circulation (Crosby and Cooney 1946) Chalmers and Davidson surveyed the use of this procedure in 14 patients and found considerable improvement in only four Lord suggests the removal of fascia thus exposing the lymphatics in the muscles and the removal of a redundant omentum to prevent plugging of the button

Therapeutic Armamentarium in Cirrhosis—Summary

Diet
- Proteins 125-150 gm , Fat 80-100 gm Carbohydrate 450 gm
- Low sodium diet—1 5 gm to 3 0gm NaCl per day

Cation Exchange Resins (Carbo Resin)—40 to 60 gm a day

Vitamins
- B Complex
  - Niacin 300 mg or more
  - Thiamine Chloride 100 mg or more
  - Riboflavin 50 mg or more
  - Pantothenic acid 50 mg or more
  - B_{12} 60 micrograms or more
- *Ascorbic Acid—50 mg or more*
- Vitamin A—10,000 u
- Vitamin K—20 mg

Lipotropic Agents
- Methionine—3-6 gm
- Choline—3 gm

Liver Extract—3 cc daily or every other day

Intravenous Fluids—10% glucose 2000-3000 cc daily

Salt Free Albumin—25-50 gm daily

Plasma—300 cc or more daily

Blood Transfusions

Antibiotics
- Aureomycin, 500 or 1000 mg daily IV
- Terramycin—same dosage as aureomycin

Hormones
- Testosterone
  - propionate in oil, 25 mg to 100 mg intramuscularly three times a week
  - methyl sulfate, 25 mg to 50 mg sublingually daily
- ACTH—10-20 mg intravenously or 80-100 mg intramuscularly daily
- Cortisone—100 mg intramuscularly daily

Sedations
- Potassium Bromide
- Barbital 0 5 gm (cautiously)
- *Paraldehyde—2-4 cc*
- Chloral Hydrate—0 5 gm
- Scopolamine—0 5 mg

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